Hospital Library
NOV 29 1940

The American Heart Journal

A Journal for the Study of the Circulation

Published Monthly Under the Editorial Direction of The American Heart Association

Vol. 20 NOVEMBER 1940 No. 5

© Am. Ht. Assn.

FRED M. SMITH.....Editor-in-Chief

Associate Editors

HUGH McCULLOCH
IRVING S. WRIGHT
HORACE M. KORNS

EDITORIAL BOARD

EDGAR V. ALLEN
CLAUDE S. BECK
HARRY GOLDBLATT
GEORGE HERRMANN
WILLIAM J. KERR
ROBERT L. LEVY
H. M. MARVIN
JONATHAN C. MEAKINS
ROY W. SCOTT
ISAAC STARR
J. MURRAY STEELE
PAUL D. WHITE
FRANK N. WILSON
CHARLES C. WOLFERTH

Published by THE C. V. MOSBY COMPANY, 3525 Pine Blvd., St. Louis, U. S. A.
Copyright 1940 by The C. V. Mosby Company

Contents on Inside Cover

The American Heart Journal

CONTENTS FOR NOVEMBER, 1940

Original Communications

The Effect of Distention of Abdominal Viscera on the Blood Flow in the Circumflex Branch of the Left Coronary Artery of the Dog. N. C. Gilbert, M.D., G. V. LeRoy, M.D., and G. K. Fenn, M.D., Chicago, Ill. ---- 519

The Effect of Transplanted Ischemic Kidneys and of Temporary, Complete, Renal Ischemia Upon the Blood Pressure of Rabbits. Myron Prinzmetal, M.D., Harvey A. Lewis, M.D., John Taggart, M.D., Howard Wilkins, M.D., and D. R. Drury, M.D., Los Angeles, Calif. ---- 525

The Role of the Arteriovenous Anastomosis in Peripheral Vascular Disease. Karl Harpuder, M.D., Irwin D. Stein, M.D., and Jacob Byer, M.D., New York, N. Y. ---- 539

Cardiac Hypertrophy Caused by Glycogen Storage Disease in a Fifteen-Year-Old Boy. William Antopol, M.D., Ernst P. Boas, M.D., William Levison, M.D., and Lester R. Tuchman, M.D., New York, N. Y. ---- 546

The Simultaneous Action of Certain Drugs on the Blood Pressure and on the Flow in the Right and Left Coronary Arteries. R. Wégria, M.D., Hiram E. Essex, Ph.D., J. F. Herrick, Ph.D., and Frank C. Mann, M.D., Rochester, Minn. ---- 557

Studies on the Auriculoventricular Conduction Time of Normal Children and of Rheumatic Children Without Signs of Rheumatic Activity. Gertrude Reyersbach, M.D., and Ann G. Kuttner, M.D., Irvington-on-Hudson, N. Y. ---- 573

The Influence of Digitalis on the Electrolyte and Water Balance of Heart Muscle. Paul K. Boyer, M.D., and Charles A. Poindexter, M.D., New York, N. Y. ---- 586

The Significance of the Position of the Subject in the Evaluation of the Electrocardiogram. L. S. Ylvisaker, M.D., and H. B. Kirkland, M.D., Newark, N. J. ---- 592

Chromatrophic Degeneration and Rupture of the Aorta Following Thyroidectomy in Cases of Hypertension. Wm. B. Kountz, M.D., and Louis H. Hempelmann, M.D., St. Louis, Mo. ---- 599

Observations on the Cardiovascular System in Myasthenia Gravis. Alberto C. Taquini, M.D., W. Trevor Cooke, M.D., and Robert S. Schwab, M.D., Boston, Mass. ---- 611

The Effect of the Intravenous Administration of Quinidine Sulfate on the Development of Ventricular Fibrillation Following Sudden Occlusion of the Circumflex Branch of the Left Coronary Artery. F. H. Smith, M.D., C. G. McEachern, M.D., and G. E. Hall, M.D., Ph.D., Toronto, Can. ---- 620

Department of Clinical Reports

Left Auricle With a Capacity of 1,695 Grams of Blood in a Case of Mitral Stenosis. Robert Lyman Nelson, M.D., Duluth, Minn. ---- 627

Long Survival Following Coronary Thrombosis. E. H. Drake, M.D., Portland, Me. ---- 634

Terminal Cardiac Mechanism in Coronary Artery Disease. Ben E. Goodrich, M.D., Detroit, Mich., and Robert J. Needles, M.D., St. Petersburg, Fla. 637

Department of Reviews and Abstracts

Selected Abstracts ---- 641

Book Review ---- 652

Announcement ---- 653

American Heart Association, Inc. ---- 654

Vol. 20, No. 5, November, 1940. The American Heart Journal is published monthly by the C. V. Mosby Company, 3523 Pine Blvd., St. Louis, Mo. Subscription Price: United States, its Possessions, Pan-American Countries, $8.50; Canada, $9.50 a year; Foreign, $9.50. Entered as Second-Class Matter at Post Office at St. Louis, Mo., under Act of March 3, 1879. Printed in the U. S. A.

The American Heart Journal

VOL. 20 NOVEMBER, 1940 NO. 5

Original Communications

THE EFFECT OF DISTENTION OF ABDOMINAL VISCERA ON THE BLOOD FLOW IN THE CIRCUMFLEX BRANCH OF THE LEFT CORONARY ARTERY OF THE DOG

N. C. GILBERT, M.D., G. V. LEROY,* M.D., AND G. K. FENN, M.D.
CHICAGO, ILL.

THE frequent occurrence of anginal pain after meals has been the subject of much comment since the first description of angina pectoris. This high incidence after meals can be explained partly by the fact that the work of the heart is increased during the earlier period of digestion. The increase has been estimated to be as much as 15 per cent to 25 per cent above the normal resting amount.[1] This extra load, or the extra load plus the increased work imposed upon the heart by any exertion after meals, calls for an increase in the blood flow to the heart muscle which the coronary arteries may be unable to accommodate, and pain results. However, there are other observations which cannot be explained by the fact that an increased minute volume flow of blood is required during digestion. The anginal attack may be relieved immediately by belching. The attack may accompany abdominal distention and may be relieved by loosening the clothing. There seems to be some relationship between anginal attacks and hernias at the esophageal hiatus of the diaphragm. It is often observed that the condition of a patient with occlusion of a coronary artery is seriously aggravated by distention of the stomach; dramatic improvement may follow relief of this distention.

Clinically, it has seemed possible to us that distention of the stomach might institute a reflex constriction of the coronary arteries. The background for this belief may be sketched briefly: (1) It is thought by most physiologists that the coronary arteries may be constricted by vasomotor nervous impulses transmitted by the vagus nerves. Experimental confirmation of this belief is found in the reports of many workers. Morawitz and Zahn[2] and Greene,[3] working with the coronary sinus outflow method, noted this relationship. Greene's de-

*Searle Research Fellow.

From the Department of Medicine, Northwestern University Medical School.
Received for publication Feb. 20, 1940.
Read November 3, 1939, at the meeting of the Central Society for Clinical Research, Chicago.

generation experiments upon the vagi are quite conclusive. Anrep[4] found the same vagus influence in his experiments with both the denervated and the innervated heart-lung preparation. Rein[5] and Hochrein and Keller[6] have employed the thermostromuhr method of the former to arrive at the same conclusion. (2) Stimulation of the stomach, as by distention, initiates afferent impulses in the vagus nerve. These are followed by efferent vagus impulses of central reflex origin. It is the latter which, in our opinion, lead to coronary vasoconstriction. This type of reaction may be considered one of the vagovagal reflexes.

EXPERIMENTAL PROCEDURE

Fifteen large, healthy dogs, which were anesthetized with dial (Ciba), or, preferably, with Gréhant's mixture, were used. A carefully calibrated thermostromuhr of the "direct current heater" type[7] was applied to the circumflex branch of the left coronary artery. The dog's chest was then closed. Continuous photographic records of the coronary blood flow and the blood pressure and pulse from a femoral artery were made. When these became stabilized, a dose of a drug known to be a coronary dilator (theobromine sodium acetate, 60 mg., aminophyllin, 50 mg., or adenylic acid, 3 mg.) was given intravenously. If the response to this medication was satisfactory, it was known that the circulatory system was capable of reacting, and that the thermostromuhr was well placed and was functioning. A large balloon was then placed in the stomach and was inflated with varying amounts of air. The best results were obtained when about 600 c.c. of air were introduced and when the intragastric pressure was raised to 10 or 15 mm. of mercury. On a few occasions a higher pressure (40 to 60 mm. of mercury) was employed, but this was less satisfactory, apparently because it produced a sudden, large increase of venous pressure. In most of the animals, several observations on the effect of stomach distention were made before and after the administration of atropine or the performance of vagotomy. In some of the animals, also, air was introduced into the

TABLE I

SUMMARY OF EXPERIMENTAL DATA

EXPERIMENT NO.	ANESTHETIC	BEFORE ATROPINE. INFLATION OF:		AFTER ATROPINE. INFLATION OF:		VAGUS SECTION			
						BEFORE		AFTER	
		STOMACH	PERITONEUM	STOMACH	PERITONEUM	STOMACH	PERITONEUM	STOMACH	PERITONEUM
		*							
1	Dial		+						
2	Dial		−						
3	Dial								++
4	Dial	−o	+						
5	Dial	−	+						
6	Dial	o+		o					
7	Dial	−+		o	+				
8	Dial	−							
9	Dial	−−+							
10	Gréhant	+−		−+					
11	Gréhant	−−							
12	Gréhant	−	−		+				
13	Gréhant	−	−	o	o				
14	Gréhant					−−		oo	
15	Gréhant					−−		o+	

*o, coronary flow unchanged after inflation of stomach or peritoneal cavity
+, coronary flow increased after inflation of stomach or peritoneal cavity
−, coronary flow decreased after inflation of stomach or peritoneal cavity

peritoneal cavity through a trocar until the abdomen was visibly distended. This was also repeated after the vagi had been sectioned or after atropine (0.0013 Gm.) had been given. Tables I and II summarize our experimental data.

TABLE II

SUMMARY OF THE DATA OF TABLE I

EXPERIMENTAL CONDITIONS	CORONARY ARTERY BLOOD FLOW:			
	UNCHANGED	INCREASED	DECREASED	TOTAL
Stomach distention before atropine or vagotomy	2	4	15	21
Stomach distention after atropine or vagotomy	5	5	1	11
Peritoneal distention before atropine or vagotomy	0	3	3	6
Peritoneal distention after atropine or vagotomy	1	4	0	5

RESULTS

The dogs' stomachs were distended twenty-one times before drugs were given or the vagi sectioned. In fifteen instances the coronary blood flow decreased. The decrease was definite, ranging from 15 per cent to 35 per cent, and was usually accompanied by little or no change in the blood pressure and pulse rate. Fig. 1 is a portion of a typical tracing from such an experiment. Marked distention of the stomach, as a matter of fact, quite frequently increased the pulse rate and the systolic blood pressure; under these circumstances, the occurrence of a

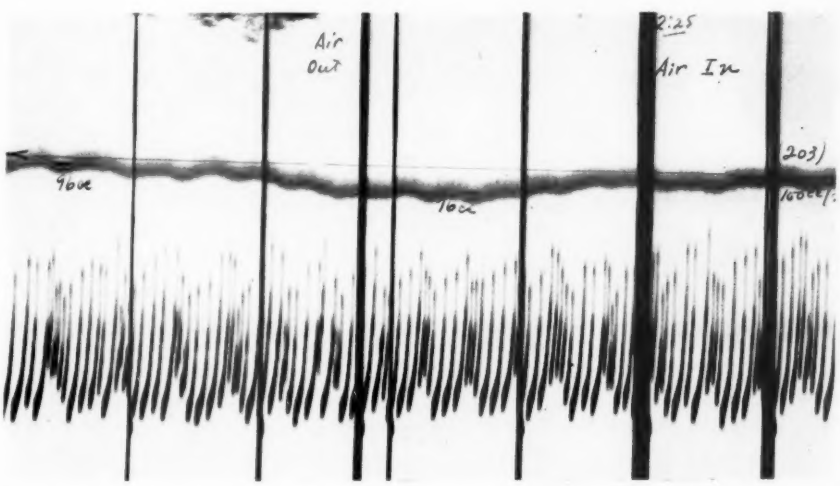


Fig. 1.—April 17, 1939, Gréhant anesthesia was used. Tracing runs from right to left.
Fig. 2.

decrease in coronary flow was especially significant. Fig. 2 was drawn from the photographic curves of a typical, complete experiment. Moderate inflation of the stomach caused the pulse rate to increase while the coronary flow remained practically unchanged. Further distention

(to 25 to 30 mm. of mercury) resulted in a distinct diminution of coronary flow, together with a distinct increase of the systolic blood pressure and the pulse rate.

After the administration of atropine, or the cutting of both vagi, the dogs' stomachs were inflated eleven times. The coronary flow decreased once, increased five times, and remained unchanged five times (Fig. 2).

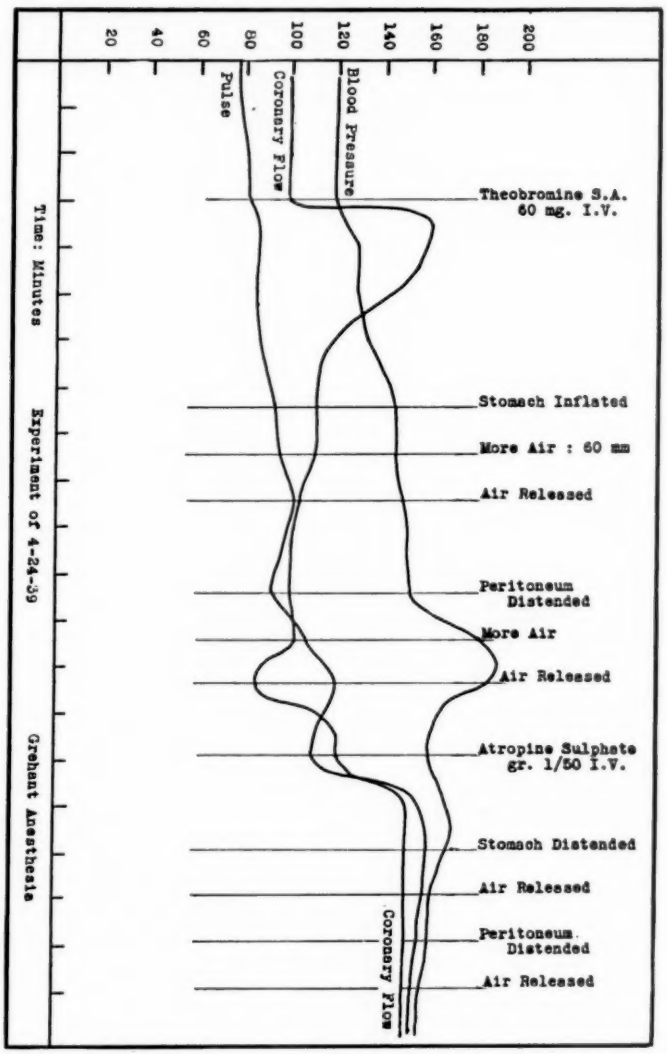


Fig. 2.

It was found that when the balloon was placed in the fundus, or partially in the cardia, the deterrent effect on the coronary flow was greater than when it was placed more centrally in the stomach. Tugging on the inflated balloon seemed to have little additional effect. This observa-

tion seems to favor our interpretation, namely, that the reduction in coronary flow is caused by reflex nervous action, rather than by mechanical displacement. Further light was cast on this point by the results which we obtained when the peritoneal cavity was distended. This was done six times before the vagi were interfered with; the coronary flow increased three times and decreased three times. The effect of this type of inflation is illustrated in Fig. 2; the blood pressure increased while the coronary flow decreased. After the administration of atropine in this experiment, the coronary flow remained unchanged when the peritoneal cavity was again inflated. After atropine administration or bilateral vagotomy, the peritoneal cavity was distended five times. The coronary flow increased in four instances and was unchanged in one.

DISCUSSION

In the absence of reflex coronary vasoconstriction, one might naturally expect that a sudden rise in the intra-abdominal pressure would increase the venous return flow to the heart. In accordance with Starling's law, and as a result of reflexes like the Bainbridge reflex, the blood pressure, pulse rate, and cardiac output should increase temporarily. Ordinarily, any or all of these three factors would augment the coronary blood flow. The fact that in many of our experiments the coronary flow decreased when augmentation should have occurred argues for a reflex coronary vasoconstriction. The abolition of this unfavorable reaction by the administration of atropine or by bilateral vagotomy would seem to implicate the vagus nerve as the mediator of the reflex. The existence, or the operation, of such a reflex is obviously disadvantageous to the heart. Previous attempts to elicit this reflex experimentally, not only in our laboratory but elsewhere, were not successful, except in the case of von Bergmann,[8] whose results parallel ours. It seems probable that unsuitable, or too deep, anesthesia or excessive distention of the viscera may have been responsible for the negative results in the past. In our present study, many experiments were quite unsatisfactory because of these factors. Furthermore, since this reflex may be only one of many influences converging, at a given time, on the coronary arteries, it is quite probable that it may frequently fail to exert an effect, or may be overwhelmed by other factors.

Finally, it is fair to conclude that if such a reflex operated at a time when the margin of reserve between the myocardium's need for blood and the coronary circulation's ability to supply it was small, an attack of angina pectoris might be precipitated.

CONCLUSIONS

1. In carefully performed experiments on dogs, using light anesthesia, distention of the stomach or peritoneal cavity initiated, in many instances (but not always, because of differences in the reactions of individual animals), a vagovagal reflex which caused a decrease in the

flow of blood through the circumflex branch of the left coronary artery.

2. The mechanism of some of the attacks of angina pectoris in patients with distended stomachs is made clear by this study.

REFERENCES

1. a. Grollman, A.: Physiological Variations in the Cardiac Output of Man, III, The Effect of the Ingestion of Food on the, etc., Am. J. Physiol. **89**: 366, 1929.
   b. Starr, I., and Collins, L. H.: Studies of the Cardiac Output in Normal Men, Am. J. Physiol. **96**: 228, 1931.
2. Morawitz, P., and Zahn, A.: Untersuchungen ueber den Coronarkreislauf, Deutsches Arch. f. klin. Med. **116**: 366, 1914.
3. Greene, C. W.: An Analysis of the Relations of the Coronary Constrictor and Dilator Nerves in the Cervical Vagosympathetic of the Dog, AM. HEART J. **11**: 592, 1936.
4. Anrep, G. V.: Lane Medical Lectures: Studies in Cardiovascular Regulation, 1936, Stanford University Press, p. 82.
5. Rein, Hermann: Die Physiologie der Herz-Kranz-Gefaesse II., Ztschr. f. Biol. **92**: 115, 1931.
6. Hochrein, M., and Keller, J.: Untersuchungen am Koronarsystem, Arch. f. exper. Path. u. Pharmakol. **159**: 312, 1931.
7. Baldes, E. J., and Herrick, J. F.: A Thermostromuhr With Direct Current Heater, Proc. Soc. Exper. Biol. & Med. **37**: 432, 1937.
8. von Bergmann, G.: Das 'epiphrenale Syndrom', seine Beziehung zur Angina pectoris und zum Kardiospasmus, Deutsche med. Wchnschr. **58**: 605, 1932.

THE EFFECT OF TRANSPLANTED ISCHEMIC KIDNEYS AND OF TEMPORARY, COMPLETE, RENAL ISCHEMIA UPON THE BLOOD PRESSURE OF RABBITS

MYRON PRINZMETAL, M.D., HARVEY A. LEWIS, M.D.,
JOHN TAGGART, M.D., HOWARD WILKINS, M.D., AND D. R. DRURY, M.D.
LOS ANGELES, CALIF.

HOUSSAY, Taquini, and their co-workers[1] have made certain observations which are of fundamental importance in the study of experimental hypertension. They were able to demonstrate that transplantation of the ischemic kidneys of dogs with Goldblatt hypertension[2] caused an almost immediate rise in the blood pressure of the recipient animal after anastomosis of the renal and carotid-jugular vessels. A more pronounced rise took place if the animals into which the transplantation was made had been previously nephrectomized. An attempt to confirm these results on another animal appeared to be of sufficient importance to justify the experiments reported in this paper.

The rabbit was chosen because, like the dog, it lends itself to the production of hypertension by means of artificial renal ischemia.[3] The hypertension in this animal appears to be identical with that in the dog; furthermore, it can be extremely severe, to the extent of attaining the so-called malignant phase, with widespread, necrotizing arteriolitis.[4]

Transplantation of Ischemic Kidneys of Hypertensive Rabbits Into the Necks of Rabbits With Normal Blood Pressure

METHOD

Hypertension was produced in rabbits by means of renal ischemia.[2, 5] Rabbits which were approximately three weeks old, and weighed between two and three hundred grams, were anesthetized with ether, and the left renal pedicle was exposed through an abdominal incision. A wire, 0.55 mm. in diameter, was placed alongside the renal artery, and a silk ligature tied snugly about both vessel and wire, after which the wire was withdrawn. When the rabbit weighed approximately 1500 grams, the healthy kidney was removed. Following the nephrectomy, a pronounced rise in blood pressure developed in most instances within the course of a few weeks, often reaching extremely high levels. These animals died as a result of widespread hemorrhage caused by vascular lesions. Only animals with a definite and persistent hypertension were used in the transplantation experiments. By palpation of the kidneys through the abdominal wall, a difference in their size could be detected with reasonable accuracy. It was found that if the ischemic kidney was too small, i.e., less than approximately 2.5 centimeters in length, removal of the normal kidney usually led to rapidly fatal uremia. On the other hand, if the length of the ischemic kidney exceeded three centimeters, unless the normal kidney was longer by about six millimeters, its removal resulted in only a small rise of blood pressure, or none at all.

Two methods were used in estimating the blood pressure. The systolic pressure in the central artery of the ear was measured by means of Grant and Rothschild's

From the Departments of Physiology and Medicine, University of Southern California Medical School.

Received for publication March 1, 1940.

Endowed by grants from the Dazian Foundation for Medical Research and the Beaumont Trust Fund.

capsule.[6] Provided certain precautions are observed, this method has proved to be very reliable.[3] The blood pressure was also measured by the Riva-Rocci method in the following way: the rabbit was tied to an animal board, a blood pressure cuff wrapped around the abdomen, and a diaphragm stethoscope placed under the cuff over the abdominal aorta. Both systolic and diastolic pressures could usually be measured by auscultation.

TECHNIQUE OF TRANSPLANTATION

It was found necessary to modify the technique described by Houssay,[1] because of the small size of the renal vessels of the rabbit. The following method was devised after many unsuccessful trials. The normal animal was anesthetized, and its head immobilized in the clamps of a specially devised frame. The latter was provided with movable arms which held the cannulas, and with an adjustable receptacle for the ischemic, "hypertensive" kidney. The anastomoses were performed in the following manner: the carotid and jugular vessels were tied and severed, and the corresponding cannulas were placed over their proximal ends, which, in turn, were slipped into position over the ends of the specially designed arms. The projecting portions of the vessels were then everted over the cannulas and securely tied; meanwhile, the vessels themselves were occluded more proximally by rubber bands. A few drops of dilute heparin solution were placed in the open lumina of the vessels to prevent coagulation. The solitary, ischemic kidney of the hypertensive animal was then removed, and the renal vessels were slipped over the corresponding carotid and jugular vessels and held firmly in place by snapping the "rings" over the cannulas. Thus an intima-to-intima anastomosis was established. The adjustable arms were then removed, to prevent undue tension on, or torsion of, the vessels, and the rubber bands released to re-establish the circulation of the transplanted kidney. The details of the technique may be seen in the accompanying diagrams (Fig. 1). The blood pressure in the femoral artery was recorded on a moving drum.

Systemic anticoagulants were not necessary, for there was an interval of only about five minutes between removal of the kidney and restoration of its circulation. If the interval was longer, clots frequently formed within the renal vessels, rendering the transplant unsuccessful. Nembutal was employed as the anesthetic agent for both donor and recipient. This drug has been found to have only a slight effect on blood pressure, and less inhibiting effect on the pressor action of the renal pressor substance than other anesthetics, as, for instance, urethane.[7] In several instances, 1 per cent chloralose in 2 per cent gum acacia solution was used because it was the anesthetic recommended by Fasciolo, et al.,[1f] but it was found to be more toxic than nembutal.

That the blood supply to the transplanted kidney was adequate was clearly indicated by the following observations. Urinary secretion was resumed in some instances as early as two or three minutes after the transplantation had been completed. One experiment was continued for eleven hours, and active secretion of urine continued during the entire period. When the carotid artery was temporarily occluded, the transplanted kidney immediately shrank in size and became soft and pale; upon release of the arterial clamp the kidney speedily regained its original size and color. When the renal or jugular vein was temporarily occluded, the kidney became engorged within two or three seconds, and became cyanotic and increased in size and firmness; upon release of the venous clamp the kidney rapidly assumed its former appearance and consistency. The injection of a small amount of epinephrine into the transplanted kidney was followed by a prompt and appreciable rise of blood pressure. When a small cut or puncture wound was made in the cortex of the transplanted kidney, arterial blood oozed from it immediately.

The following successful transplantations were made: *Group 1.*—Kidneys of hypertensive rabbits were transplanted into eleven animals that

had normal blood pressures. In five, bilateral nephrectomy had been performed twenty-four to forty-eight hours previously; in the remaining six, the kidneys had not been removed. *Group 2.*—In two instances, normal kidneys were removed and kept at temperatures of 22° and 37° C., respectively, for a period of two hours before transplantation.

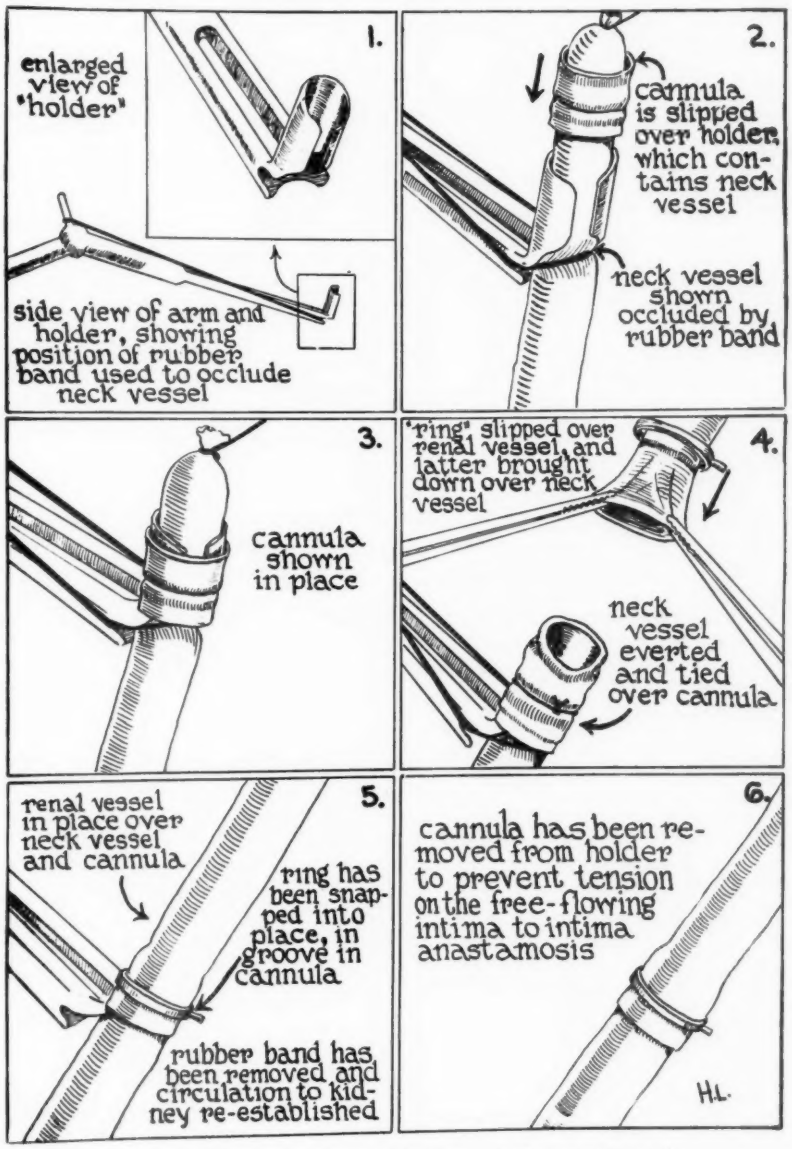

1.
enlarged view of "holder"
side view of arm and holder, showing position of rubber band used to occlude neck vessel
2.
cannula is slipped over holder, which contains neck vessel
neck vessel shown occluded by rubber band
3.
cannula shown in place
4.
"ring" slipped over renal vessel, and latter brought down over neck vessel
neck vessel everted and tied over cannula
5.
renal vessel in place over neck vessel and cannula
ring has been snapped into place, in groove in cannula
rubber band has been removed and circulation to kidney re-established
6.
cannula has been removed from holder to prevent tension on the free-flowing intima to intima anastamosis
HL.

Fig. 1.—Details of technique of intima-to-intima anastomosis.

In these kidneys, clotting was prevented by washing out the blood immediately with Ringer's solution. *Group 3.*—In five experiments, kidneys of nonhypertensive rabbits were transplanted into normal animals.

RESULTS

In ten of the eleven experiments *(Group 1)*, transplantation of the "hypertensive," ischemic kidneys produced an immediate, but transient, fall in blood pressure of 10 to 20 mm. of mercury. The pressure gradually returned to its previous level in almost all instances (Fig. 2, Table I), but did not exceed the control level in a single animal (measurements were made over periods of ten minutes to eleven hours following reestablishment of the circulation). In the eleventh animal the blood pressure rose about 10 mm. Hg, and maintained the higher level for about fifty minutes. In this experiment the kidneys had not previously been removed (Table I).

TABLE I

EFFECT ON BLOOD PRESSURE OF TRANSPLANTED ISCHEMIC KIDNEYS FROM HYPERTENSIVE RABBITS

ANIMAL	B.P. BEFORE HYPERTENSION	B.P. AT TIME OF TRANSPLANTATION	DURATION OF HYPERTENSION	EVIDENCE OF MALIGNANT HYPERTENSION	ALTERATION OF RECIPIENT'S B.P. AFTER TRANSPLANTATION	VENTRICLE WT. / BODY WT.	× 10^3
Normal recipients							
RA 74	120/85	180/140	76 days	0	Transient fall of 5-10 mm.	9.3 / 3,150	296
RA 83	–	194/160	72 days	0	Transient fall of 5-10 mm.	9.1 / 3,250	2.80
RA 51	–	210/160	169 days	0	Transient fall of 5-10 mm.	10 / 2,680	3.74
RA 107	–	240/200	43 days	+	10 mm. rise in 30 secs.	6.6 / 2,080	3.18
RA 118	140/90	230/190	16 days	+	Transient fall of 5-10 mm.	5.8 / 2,350	2.50
Nephrectomized recipients							
RA 102	130/100	220/170	65 days	+	Transient fall of 5-10 mm.	9.8 / 3,155	3.12
RA 117	130/85	204/160	12 days	+	Transient fall of 5-10 mm.	6.2 / 2,060	3.00
RA_2 28	135/100	174/114	36 days	0	Transient fall of 5-10 mm.	7.4 / 2,975	2.44
RA_2 17	–	220/150	11 days	+	Transient fall of 5-10 mm.	6.8 / 2,090	3.25
R 13	–	220/190		+	Transient fall of 5-10 mm.		
Average							3.01*

*Average for ten normal rabbits selected at random was 2.43.

Completely negative results were also obtained in the two instances in which totally ischemic kidneys were transplanted *(Group 2)*, and in the five in which normal kidneys were transplanted *(Group 3)*.

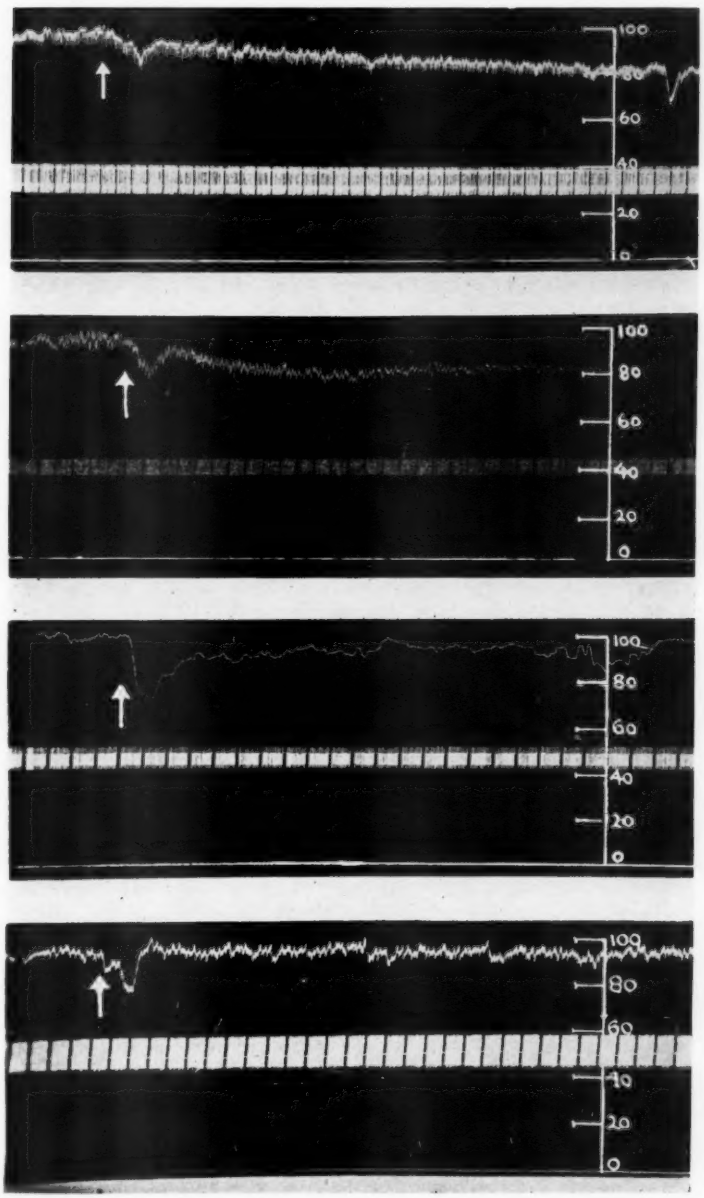


Fig. 2.—Effect of transplanted ischemic kidney on recipient's blood pressure. Circulation of kidney re-established at point of arrow. No rise in blood pressure. Time marker, 15-second intervals.

DISCUSSION

It may be seen that in only one of eleven rabbits was transplantation of the ischemic kidney followed by a rise in blood pressure, and that the elevation in this solitary instance was of small magnitude and short

duration. In view of the negative results in the other ten experiments, it is possible that this rise represented a spontaneous variation of the blood pressure, unrelated to the transplantation.

Considering the consistent and definite elevation reported by Houssay and his coworkers,[1] it is difficult to explain the failure of the blood pressure to rise in these experiments. For the following reasons, the objection cannot be made that our rabbits did not show a sufficient degree of hypertension.

1. Only rabbits which exhibited a significant and persistent elevation of blood pressure were employed, and the readings were checked by two different methods, as described above.

2. In six of the eleven animals the malignant phase of hypertension had been reached, for necrotizing arteriolitis was found in the post-mortem histologic sections. These animals were sacrificed only a short time before they were expected to die as a result of their hypertension.

3. In all instances the heart weights indicated definite cardiac hypertrophy (Table I).

Moreover, it cannot be argued that the transplanted kidneys did not receive an adequate blood supply; evidence concerning this point has already been presented.

The Effect Upon the Blood Pressure of Re-establishing the Circulation of Completely Ischemic Kidneys

In view of the negative results of the first series of experiments, an effort was made to confirm in rabbits the following observation of Taquini and his co-workers.[8] After clamping the renal pedicles of dogs for six or seven hours, and re-establishing the circulation by removing the clamps, they noted an immediate and conspicuous rise of blood pressure, an observation which we have confirmed on dogs and cats.[9]

METHODS AND RESULTS

Three series of experiments were carried out. In the first series, seven rabbits were anesthetized with nembutal, the abdomen was opened, and the right kidney removed. The left kidney was then freed from all attachments except the pedicle, and a bulldog clamp was placed across the renal artery, renal vein, and ureter. The abdomen was then closed, and the animal allowed to recover from the anesthetic. Three to five hours later the animal was again anesthetized with nembutal, the carotid was cannulated, and the blood pressure was recorded continuously. The abdomen was then reopened and the clamp released. In no instance was there a rise in blood pressure above the control level (Fig. 3, Table II).

In these experiments it was important to satisfy two requirements: (1) there should be no circulation in the kidneys while the clamps were

in place, and (2) an adequate circulation should be re-established upon removal of the clamps. Whether or not the first requirement was fulfilled was ascertained by puncturing the cortex after the pedicle had been clamped; failure to bleed or slight venous oozing was taken to indicate cessation of the renal circulation.

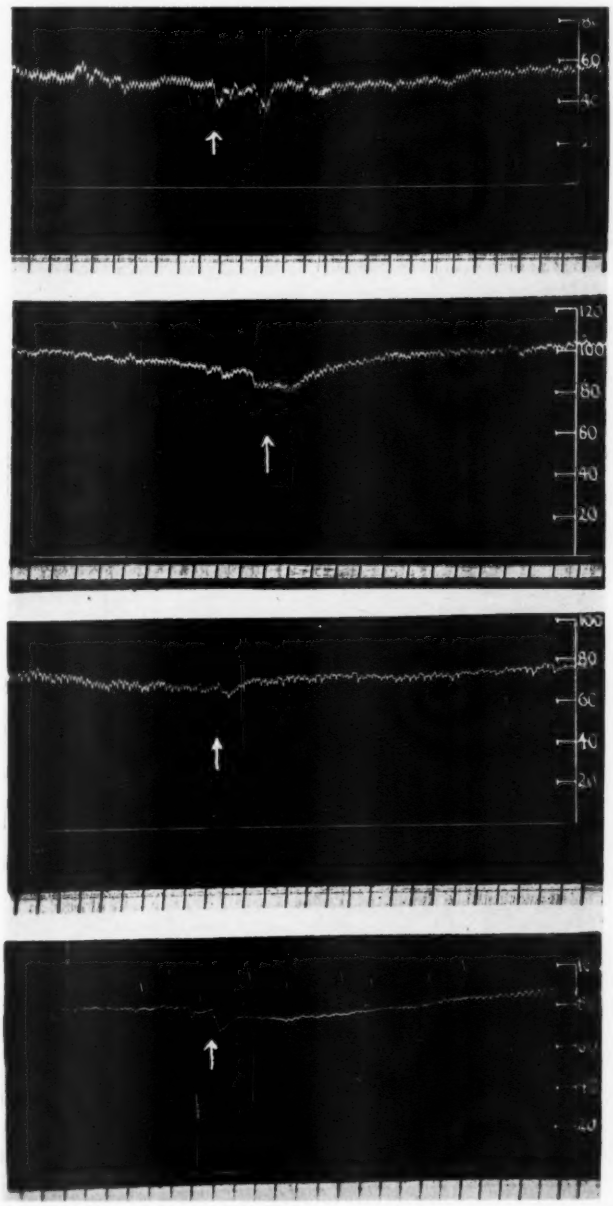


Fig. 3.—Effect on blood pressure of clamping left renal pedicle. Right kidney previously removed. Clamp removed at point of arrow. No rise of blood pressure. Nembutal anesthesia. Time marker, 15-second intervals.

TABLE II

EFFECT ON BLOOD PRESSURE OF RE-ESTABLISHING CIRCULATION IN COMPLETELY ISCHEMIC KIDNEYS. PEDICLE LEFT KIDNEY CLAMPED; RIGHT KIDNEY REMOVED. NEMBUTAL ANESTHESIA

ANIMAL	TIME CLAMPED	RISE OF B. P.	FALL OF B. P.	RISE OF B. P. ON INJECTION OF EPINEPHRINE INTO KIDNEY	RECLAMPED	RISE OF B. P. ON SECOND INJECTION OF EPINEPHRINE INTO KIDNEY	RISE OF B. P. ON INTRAVENOUS INJECTION OF EPINEPHRINE
C 1	5 hr.	0	0	+			+
C 2	5 hr.	0	0	+			+
C 3	5 hr.	0	0	+			+
C 4	5 hr.	0	0	+			+
C 5	3 hr.	0	0		+	+	+
C 6	4 hr.	0	0		+	+	+
C 7	6 hr.	0	0		+	+	+

In three experiments, after it had been noted that removal of the clamp was not followed by an elevation of the blood pressure, the pedicle was again clamped. After three hours, 0.2 mg. of epinephrine was injected into the ischemic kidney. During the next few minutes no rise in blood pressure occurred; the clamp was then removed for the second time, and immediately there was an epinephrine pressor reaction (Fig. 4, Table II). When a like amount of epinephrine was injected intravenously after the blood pressure returned to normal, the resulting pressor effect was usually similar to that which followed the previous injection into the kidney. Failure of the blood pressure to rise after the injection of epinephrine into the kidney while the clamp was in place indicated that, if there was any renal circulation at the time, it was too minute to wash out a detectable amount of epinephrine into the general circulation. By the same token, the rise in pressure following release of the clamp demonstrated that the renal circulation had been restored. These experiments indicated that if a sufficient amount of pressor substance of the nature of epinephrine had accumulated in the kidney during the period of ischemia, a systemic pressor reaction would have occurred upon re-establishment of the renal circulation.

It has been demonstrated that anesthesia of any type interferes with the pressor effects of renin.[7] In order to exclude the possibility that anesthesia interfered with pressor responses in the above experiments, a second series of ten experiments was performed upon unanesthetized rabbits in the following manner. Under ether anesthesia, the abdomen was opened, the right kidney removed, and the left kidney freed from all attachments except the pedicle. A rubber band lubricated with vaseline was looped around the pedicle, and the ends of the rubber band were left extruding through a stab wound in the loin. To the center of this elastic loop was tied a ligature which, in turn, led through the abdominal wall. The rubber band was then pulled taut enough to

occlude the vessels of the pedicle, and tied externally with a silk ligature. That the constriction of the pedicle was effective was shown by the fact that there was no bleeding, or only slight venous oozing, when the cortex was punctured. In three of the six experiments in which this technique was followed the ligature was placed only about the renal artery. The animals were then allowed to recover from the anesthetic. Three to seven hours later, the blood pressure in the rabbit's ear was estimated by means of Grant and Rothschild's capsule, according to the method previously mentioned.[3] After a constant baseline had been established, the ends of the rubber band were cut, and the loop was pulled from the

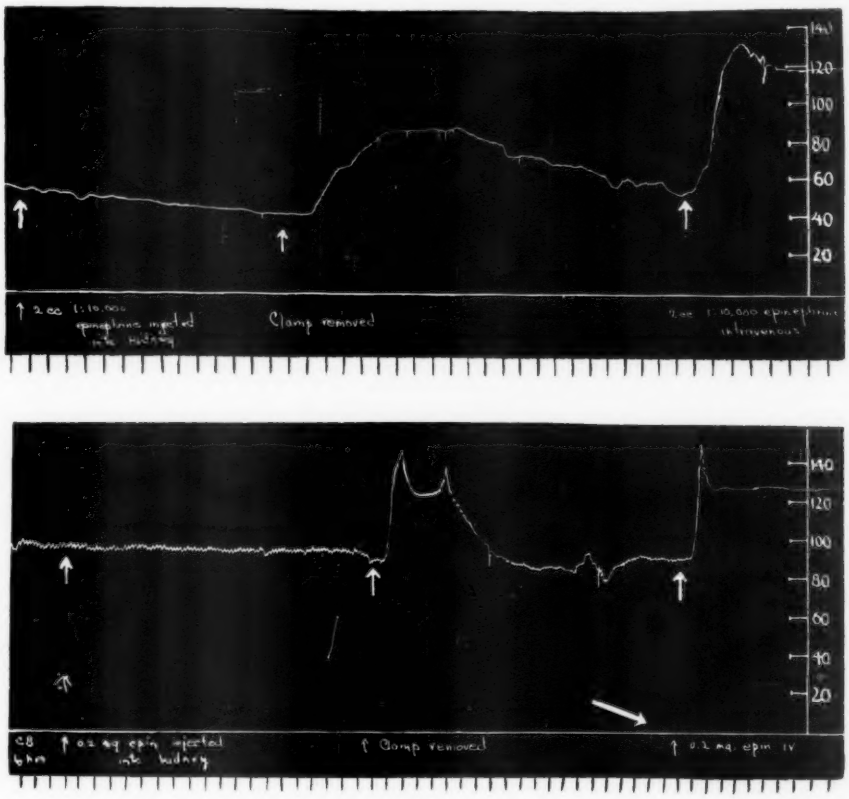


Fig. 4.—Experiments to show that renal circulation had ceased while clamp was in position and satisfactorily re-established after clamp was removed. Same animals as in Fig. 3. At first arrow, with clamp in place, 0.2 mg. epinephrine injected into kidney. No rise in blood pressure. At second arrow, clamp removed. Typical epinephrine pressor response. At third arrow, 0.2 mg. epinephrine intravenously. Similar pressor response. Nembutal anesthesia. Time marker, 15-second intervals.

pedicle by traction on the ligature leading through the abdominal wall. This procedure took no more than thirty seconds, and caused no discomfort to the animal. Blood pressure observations were made every fifteen seconds for at least ten minutes after releasing the ligature. No rise of blood pressure was observed (Fig. 5, *B*, Table III).

TABLE III

EFFECT ON BLOOD PRESSURE OF RE-ESTABLISHING CIRCULATION IN COMPLETELY ISCHEMIC KIDNEYS. LEFT RENAL ARTERY OR PEDICLE CLAMPED. RIGHT KIDNEY REMOVED. NO ANESTHESIA UPON RELEASE OF CLAMP.

ANIMAL	PROCEDURE	TIME OCCLUDED	RISE OF B. P.	FALL OF B. P.	TESTS OF RENAL CIRCULATION	RISE OF B. P. ON INJECTION OF EPINEPHRINE INTO KIDNEY	KIDNEY HEPARINIZED
CA 4	Silk ligature over whole pedicle	7 hr.	0	0	Vein and artery filled out, each bled, as did cortex on puncture	+	
CA 6	Silk ligature over whole pedicle	3½ hr.	0	0	Vein and artery filled out, each bled, as did cortex on puncture	+	
CA 8	Silk ligature over whole pedicle	4 hr.	0	0	Vein and artery filled out, each bled, as did cortex on puncture	+	
CA 13	Rubber band about renal artery	4½ hr.	0	0	Vein and artery filled out, each bled, as did cortex on puncture	+	
CA 14	Rubber band about renal artery	3½ hr.	0	0	Vein and artery filled out, each bled, as did cortex on puncture	+	+
CA 16	Rubber band about renal artery	6½ hr.	0	0	Vein and artery filled out, each bled, as did cortex on puncture	+	+
CA 18	Rubber band about entire pedicle	4¾ hr.	0	0	Vein and artery filled out, each bled, as did cortex on puncture		
CA 20	Rubber band about entire pedicle	3½ hr.	0	0	Vein and artery filled out, each bled, as did cortex on puncture		
CA 21	Rubber band about entire pedicle	7 hr.	0	0	Vein and artery filled out, each bled, as did cortex on puncture	+	+
CA 22	Rubber band about entire pedicle	5¼ hr.	0	0	Vein and artery filled out, each bled, as did cortex on puncture	+	+

It was observed in many of the experiments, upon examining the kidneys during life and post mortem, that thrombi had formed in the renal veins. Obviously, such experiments had to be discarded, and, in view of the fact that thrombi could sometimes not be detected at the operation, it was deemed necessary to perform a test which would prove that the renal circulation had been satisfactorily reestablished. For this purpose, after taking the blood pressure in the ear of the unanesthetized rabbit, anesthesia with nembutal was induced, the carotid artery was

cannulated, and the blood pressure recorded on a smoked drum. The abdomen was then reopened, and 0.025 mg. of epinephrine was injected into the kidney. If a well-defined rise in blood pressure took place, it was concluded that the circulation had been adequately re-established. When thrombosis had developed, the blood pressure rose slightly, or not at all, in response to the injection of epinephrine.

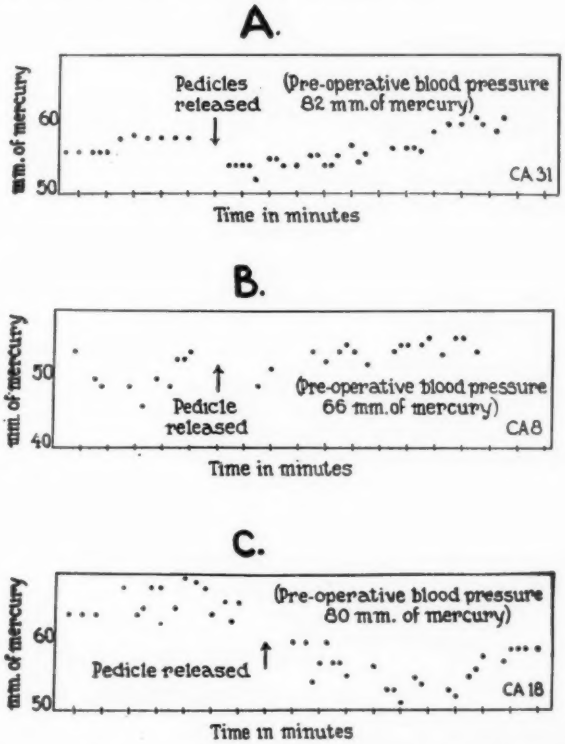


Fig. 5.—Effect on blood pressure of re-establishment of renal circulation in unanesthetized rabbits. *A*, Both renal pedicles clamped. *B*, Left renal pedicle clamped. Right kidney removed. *C*, Same as *B*, except for injection of heparin into renal artery to prevent clot formation. No rise of blood pressure in any case after release of clamp.

In almost all instances, whether or not the injection of epinephrine was followed by a pronounced rise in blood pressure, the kidneys usually assumed a distinctly abnormal aspect, i.e., they became edematous, congested, and hemorrhagic. It was thought that these abnormalities might be caused by thrombosis of some of the smaller vessels, and, for this reason, the following supplementary experiments were performed on four rabbits. The abdomen was opened under ether anesthesia, and the right kidney removed as before. The left kidney was freed of all its attachments except the pedicle, and the renal artery and vein were carefully separated. A loose ligature was placed about the renal artery in such a way that traction would occlude the vessel. While traction was thus maintained on the ligature, a small needle was introduced

into the arterial lumen close to the kidney, and a bulldog clamp placed across the renal vein. A solution of 50 mg. of heparin in 0.6 c.c. of physiologic salt solution was then quickly injected into the artery, the clamp was shifted so that it would occlude the entire pedicle, and the arterial ligature and needle were removed. Successful injection of the heparin into the lumen of the artery was signalized by immediate blanching of the cortex. The lubricated rubber band which had previously been placed loosely about the pedicle was tightened externally from the loin until the vessels were occluded; the bulldog clamp was removed, and the rest of the procedure was the same as in the experiments on nonheparinized kidneys. The animal was then allowed to recover from the anesthetic, and the experiment was completed in the manner described above. No elevation of blood pressure resulted (Fig. 5, *C*, Table III).

A third series of experiments was performed. These were similar in every detail to those of the second series, except that the pedicles of both kidneys were clamped. Four such experiments were performed; the criteria of success were the same as those previously described. (See Fig. 5, *A*, and Table IV.)

TABLE IV

EFFECT ON BLOOD PRESSURE OF RE-ESTABLISHING CIRCULATION IN COMPLETELY ISCHEMIC KIDNEYS, BOTH PEDICLES CLAMPED. NO ANESTHESIA UPON RELEASE OF CLAMP

ANIMAL	PROCEDURE	RISE OF B. P.	FALL OF B. P.	TESTS OF RENAL CIRCULATION	RISE OF B. P. ON INJECTION OF EPINEPHRINE INTO KIDNEYS
CA 23	Bilateral occlusion	0	0	Vein, artery, and cortex bled	+
CA 27	Bilateral occlusion	0	0	Vein, artery, and cortex bled	
CA 30	Bilateral occlusion	0	0	Vein, artery, and cortex bled	+
CA 31	Bilateral occlusion	0	0	Vein, artery, and cortex bled	+

RESULTS

In no instance did a rise in blood pressure take place in any of the three series of experiments. (See Figs. 3 and 5, and Tables II, III, and IV.)

DISCUSSION

In view of the positive results with dogs and cats,[1, 9] it is difficult to explain the failure to obtain pressor effects in these experiments on rabbits. The most logical explanation appears to be that there is a species difference, but the reasons for this difference are not easy to

comprehend because of the fact that the hypertension in all three experimental animals appears to be identical. Although it is quite clear that the mechanism of the hypertension in dogs is humoral rather than vasomotor, it seems probable that this is true also of the rabbit, for Pickering and one of us[10] found that the blood flow in the ears of hypertensive rabbits is not increased by depriving the blood vessels of their nerve supply, as would be the case if the hypertension were of vasomotor origin.

CONCLUSIONS

1. A new technique for establishing an intima-to-intima anastomosis is described.

2. Transplantation of the ischemic kidneys of hypertensive rabbits into normal animals was performed six times, and into nephrectomized animals with normal blood pressure five times.

3. In no instance was there a significant change in the blood pressure following the transplantation.

4. Complete ischemia of one kidney (after the opposite kidney had been extirpated) was produced in two series of experiments on rabbits by clamping the renal pedicle. In the first series, seven animals were anesthetized with nembutal; in the second series, six animals were unanesthetized. In a third series of four unanesthetized animals, unilateral nephrectomy was not performed, and both kidneys were made ischemic by clamping the renal pedicles.

5. In none of the seventeen animals in these three series of experiments did a rise in blood pressure occur after the clamps on the pedicle or pedicles were released.

6. In a supplementary series of four experiments, heparin was injected into the renal artery to prevent clotting during the period of total ischemia. When the clamp was released, there was no rise in blood pressure.

7. The difference between the response of rabbits and that of dogs and cats is probably an example of species variation.

REFERENCES

1. a. Houssay, B. A., and Fasciolo, J. C.: Secreción hipertensora del riñón isquemiado, Rev. Soc. argent. de biol. **13:** 284, (Oct.) 1937; abstr.: Sécrétion hypertensive du rein ischémié, Compt. rend. Soc. de biol. **127:** 147, 1938.

b. Houssay, B. A., and Taquini, A. C.: Acción vasoconstrictora de la sangre venosa del riñón isquemiado, Rev. Soc. argent. de biol. **14:** 5, 1938; abstr.: Action vasoconstrictrice du sang veineaux du rein ischémié, Compt. rend. Soc. de biol. **128:** 1125, 1938.

c. Houssay, B. A., and Taquini, A. C.: Especificidad de las acción vasoconstrictora de la sangre venosa del riñón isquemiado, Rev. Soc. argent. de biol. **14:** 86, 1938; abstr.: Spécificité de l'action vasoconstrictrice du sang veineaux du rein ischémié, Compt. rend. Soc. de biol. **129:** 860, 1938.

d. Fasciolo, J. C.: Papel de las glandulas adrenales en la génesis de la hipertensión arterial por isquemia renal, Rev. Soc. argent. de biol. **14:** 25, 1938; abstr.: L'hypertension artérielle par ischémié rénale ne dépend pas des surrénales, Compt. rend. Soc. de biol. **128:** 1130, 1938.

e. Fasciolo, J. C.: Acción del riñón sano sobre la hipertensión arterial por isquemia renal, Rev. Soc. argent. de biol. **14:** 15, 1938; abstr.: Action du rein sain sur l'hypertension artérielle par ischémié rénale, Compt. rend. Soc. de biol. **128:** 1129, 1938.

f. Fasciolo, J. C., Houssay, B. A., and Taquini, A. C.: Blood Pressure Raising Secretion of Ischemic Kidney, J. Physiol. **94:** 281, 1938.

2. Goldblatt, H., Lynch, J., Hanzal, R. F., and Summerville, W. W.: Studies on Experimental Hypertension. I. The Production of Persistent Elevation of Systolic Blood Pressure by Means of Renal Ischemia, J. Exper. Med. **59:** 347, 1934.
3. Pickering, G. W., and Prinzmetal, M.: Experimental Hypertension of Renal Origin in the Rabbit, Clin. Sc. **3:** 357, 1938.
4. Wilson, C., and Pickering, G. W.: Acute Arterial Lesions in Rabbits With Renal Hypertension, Clin. Sc. **3:** 343, 1938.
5. Drury, D. R.: The Production by a New Method of Renal Insufficiency and Hypertension in the Rabbit, J. Exper. Med. **68:** 693, 1938.
6. Grant, R. T., and Rothschild, P.: A Device for Estimating Blood Pressure in the Rabbit, J. Physiol. **81:** 265, 1934.
7. Pickering, G. W., and Prinzmetal, M.: Some Observations on Renin, a Pressor Substance Contained in Normal Kidney, Together With a Method for Its Biological Assay, Clin. Sc. **3:** 211, 1938.
8. Taquini, A. C.: Liberacion de substancia hipertensora en el riñón completamente isquemiado, Rev. Soc. argent. de biol. **14:** 422, 1938; abstr.: Production de substance hypertensive par le rein ischémié, Compt. rend. Soc. de biol. **130:** 459, 1938.
9. Lewis, Harvey A., Leo, Sidney D., and Prinzmetal, M.: In press, AM. HEART J.
10. Pickering, G. W., and Prinzmetal, M.: Unpublished observations.

THE ROLE OF THE ARTERIOVENOUS ANASTOMOSIS IN PERIPHERAL VASCULAR DISEASE

KARL HARPUDER, M.D., IRWIN D. STEIN, M.D., AND JACOB BYER, M.D.
NEW YORK, N. Y.

INTRODUCTION

MANY years ago, anatomists (Sucquet,[1] in 1862, and Hoyer,[2] in 1877) called attention to the presence of direct connections between the arterioles and venules just before these vessels enter the capillary bed. Their widespread distribution over many surface areas, especially of the fingers and toes, and in internal organs as well, has since been repeatedly demonstrated.[3, 4, 5, 6] The best and most comprehensive review of the literature, to date, is that of Clark, published in 1938.[7]

For all practical purposes, however, it is only since the minute and careful histopathologic studies of Masson[8] and Popoff,[9] and the clinical work of Lewis and his school, that sufficient interest has been aroused to bring the arteriovenous anastomosis out of the dustbin of anatomic curiosities. Masson, in his classic papers, focused interest on the relationship of the arteriovenous anastomoses to so-called "glomus tumors." Popoff demonstrated their importance in various other pathologic conditions, especially inflammations and diseases of the blood vessels. Although he describes in great detail the histologic changes produced in the glomus* by arteriosclerosis and thromboangiitis obliterans, the point he stresses is that these diseases eventually turn the anastomosis from an active, contractile vessel into a permanently patent channel through which blood flows uncontrolled, directly into the venules. To obtain chemical proof of this assertion, he studied the blood gases in one case of thromboangiitis obliterans. The oxygen content of venous blood from the affected foot was definitely higher than that from the arm. Only the shunting of unused arterial blood, in his opinion, could explain this difference.

It was our purpose to investigate the role of the arteriovenous anastomosis in peripheral vascular disease by thoroughly examining the blood for its content of certain metabolites. Since these substances are either produced or consumed locally, the results may be considered a measure of the efficiency of the local blood supply.

METHOD OF STUDY

Goldschmidt and Light[10] and Looney and Childs[11] have shown that the composition of the blood gases is greatly influenced by various physical factors. However,

Received for publication Feb. 23, 1940.

From the Laboratories of the Medical Division, Montefiore Hospital, New York.

*Glomus, as used by Popoff, includes not only the anastomosis, but also the afferent arteriole, collecting system of veins, and the surrounding neuromuscular network.

standardization of procedure and a knowledge of the accuracy and limitations of the analytical methods which we employed enable us to attach significance to our comparative results.

The patient was kept at complete rest for at least one-half hour, about three to four hours after a light morning meal. His arm and leg were kept uncovered and dependent, and the room temperature was maintained between 69° and 72° F. Blood was withdrawn, without using a tourniquet, from a prominent antecubital vein or from the vein behind the malleolus at the ankle. The syringe in which it was collected contained a thick layer of mineral oil, and the tube in which it was stored, under anaerobic conditions, contained a column of oil at least 2 inches thick. Analysis of the blood samples was done immediately, in duplicate. The results of the two analyses usually differed no more than 0.2 to 0.3 volume per cent. If the difference exceeded 0.5 volume per cent, a third analysis was made.

The oxygen content, oxygen capacity, carbon dioxide content, and lactic acid content of the blood were ascertained by the gasometric methods of Van Slyke and Peters.[12]

Although glucose, urea nitrogen, nonprotein nitrogen content, and carbon dioxide combining power were ascertained in many cases, the results obtained were so inconstant and inconclusive that further study of these substances was abandoned.

COMPARISON OF ARM AND FOOT BLOOD

In this first group of experiments, blood from a region with an adequate (checked by the usual methods) circulation—the arms—was compared with that from a region with greatly impaired circulation—the lower extremities. Nearly all of the patients had advanced peripheral arteriosclerosis; a few had thromboangiitis obliterans. They were all patients whose vascular disease had been present for years, and all gave the usual history of intermittent claudication, or pain at rest. Typical rubor, pallor, and dependent cyanosis were present. Pulsations in the vessels of the lower extremity were very feeble or absent; this was substantiated by oscillometric readings. In all cases the skin temperature of the legs was lower (3° to 11° F.) than that of the arms. Many of the patients had diabetes, and in one or two cases the vascular disease was complicated by peripheral neuritis.

TABLE I

COMPARISON OF FOREARM AND FOOT BLOOD IN PERIPHERAL VASCULAR DISEASE

EXP.	O_2 CONTENT		CO_2 CONTENT		LACTIC ACID		O_2 CAPACITY	
	ARM	FOOT	ARM	FOOT	ARM	FOOT	ARM	FOOT
1	15.2	18.7	52.0	49.9	14.2	17.7		
2	18.0	20.2	52.8	52.0	10.0	15.1		
3	9.8	18.1	53.8	48.3	12.5	13.9		
4	16.3	18.1	50.0	49.7	16.7	18.0		
5	11.4	19.5	50.0	44.3	15.6	17.2		
6	10.5	12.6	51.8	50.4	14.1	14.5		
7	16.4	17.8	49.4	46.9	12.7	13.9	19.2	18.5
8	6.9	12.8	55.8	51.2	11.6	22.3	18.5	18.1
9	12.6	18.9	54.9	49.9	12.8	15.1	21.7	21.7
10	9.7	12.3	55.8	56.3	9.5	9.5	20.7	20.7
11	13.7	16.1	58.3	57.1	18.0	19.5	20.3	18.7
12	16.7	18.9	46.7	43.7	11.6	17.7	21.6	22.1
13	10.5	11.2	52.8	51.1	11.4	13.4	19.4	20.8
14	13.3	13.3	56.0	54.7	13.9	16.5	17.0	17.9
15	17.0	17.0	51.5	52.7	14.2	15.0	19.4	20.5

The results are presented in Table I. The oxygen content of the venous blood from the lower extremities in thirteen of the fifteen cases of peripheral vascular disease was significantly higher than that from the forearms. This is all the more surprising because, as has been noted, pain, cyanosis, and the cold, clammy skin of the involved extremities indicated how inadequate was the peripheral circulation, and how precarious was the prognosis for that limb. In the other cases, the oxygen content of arm and foot blood was identical.

The difference in oxygen content varied from 0.7 volume per cent to 8.3 volumes per cent. The highest values, curiously enough, were obtained in certain cases in which the disease was farthest advanced. The fact that the oxygen capacity of the blood was practically constant indicates quite conclusively that the disparity in the oxygen content of the arm and foot blood was the result of a difference in arterialization, not in concentration of hemoglobin.

TABLE II

COMPARISON OF FOREARM AND FOOT BLOOD IN NORMAL PEOPLE

EXP.	O_2 CONTENT		CO_2 CONTENT		LACTIC ACID		O_2 CAPACITY	
	ARM	FOOT	ARM	FOOT	ARM	FOOT	ARM	FOOT
1	17.7	16.9	47.5	46.0	16.0	15.8		
2	18.8	17.0	51.4	51.2	15.9	14.1		
3	11.8	14.4	53.5	52.0	14.8	15.0		
4	16.7	17.4	46.9	43.0	10.1	12.0		
5	15.7	15.4	49.2	49.2	14.5	14.5	20.5	20.4
6	12.4	14.9	53.0	50.0	11.0	16.5	21.0	21.2
7	16.8	13.2	51.2	51.8	12.6	13.5	20.2	20.0
8	18.3	17.8	49.9	50.5	11.8	12.1	21.0	21.1
9	17.2	16.6	53.2	53.0	19.7	19.7	19.1	19.0
10	11.5	12.2	50.8	50.3	18.6	17.8	18.2	18.9
11	14.0	16.0	52.7	51.4	10.1	11.5	17.1	18.5
12	12.1	11.5	58.1	50.9	14.4	14.8	18.0	17.5
13	14.2	11.0	52.8	53.2	8.6	8.6	16.3	16.7
14	8.2	7.1	62.6	63.0	15.6	15.5	19.4	20.1
15	18.0	14.5	51.6	51.4	9.0	11.9	20.7	20.6

In sharp contrast were the values found in a group of normal adults who were used as controls (Table II). There was no definite trend; in five cases the oxygen content of the foot blood was slightly higher, in five other cases the values were essentially the same, and in the remaining five the oxygen content of the foot blood was lower than that of the arm blood. Such differences are to be expected and are an index of the variability of response of normal persons to the same physiologic conditions. They do serve the purpose of emphasizing still further the significance of the results obtained in the first group.

As was to be expected, the values for the carbon dioxide content varied, in general, in the opposite direction to those for oxygen. In a number of cases, however, the differences in the carbon dioxide content of the venous blood from the arm and foot were not as marked as were the disparities between the oxygen values.

There were changes in the other constituents of the peripheral blood, but they were of the same degree and in the same direction in both groups, so that generalizations cannot be drawn. A remark must be made about the values for lactic acid in the venous blood from the diseased extremities. These showed a definite tendency to be near the upper limit of normal, or even above normal.

EFFECT OF EXERCISE

In the next series of experiments, twelve patients with peripheral vascular disease were used. Samples of blood from the lower extremity were first obtained in the usual manner. Then each subject was made to extend and flex the toes, slowly, but forcefully, twenty times. The needle was kept in the vein during this time, and, towards the end of the exercise period, another blood sample was collected.

TABLE III

EFFECT OF EXERCISE IN PERIPHERAL VASCULAR DISEASE

EXP.	O_2 CONTENT		CO_2 CONTENT		LACTIC ACID		O_2 CAPACITY	
	REST	EXERCISE	REST	EXERCISE	REST	EXERCISE	REST	EXERCISE
1	11.6	8.2	51.6	55.8	20.0	26.7		
2	15.6	8.7	50.8	56.6	29.8	35.3		
3	15.8	8.5	54.9	58.1	19.1	32.7	21.4	21.4
4	20.8	12.7	46.8	56.5	18.3	25.3		
5	10.6	8.2	48.2	55.5	18.1	24.4	20.2	19.6
6	18.3	17.4	48.8	49.4	12.1	19.5	18.9	18.9
7	14.3	9.2	54.4	57.7	16.7	22.5	17.5	17.4
8	14.4	14.2	55.8	58.5	17.9	18.5		
9	13.5	14.8	56.4	58.8	22.2	37.4		
10	8.4	9.4	64.3		23.8	34.8		
11	9.2	10.4	49.4	49.4	18.1	24.4	19.4	19.5
12	9.3	10.8	56.8	58.2	35.0	63.0	21.9	21.8

The most constant result of exercise was a pronounced rise of lactic acid above the basic level, which was already a high normal, or even above normal. Only in this respect did the results differ from what ordinarily occurs in normal subjects after exercise.

In eight cases, a drop in the oxygen content coincided with the exercise. Utilization of oxygen during the performance of work, is, of course, to be expected. Of more significance, however, was the fact that in four cases there was, instead of this expected result, a slight but distinct rise in the oxygen content of the peripheral blood. This rise was coupled with a marked elevation of the lactic acid content. The significance of these changes will be made clear later.

RECOVERY AFTER EXERCISE

In a third, and final, group of experiments, ten patients with peripheral vascular disease were made to exercise as before, i.e., contract the toes, slowly and forcefully, twenty times. Samples of blood from the same ankle vein were withdrawn immediately after the exercise, and

again following a rest period of one-half to one hour. During this interval, the foot was kept relaxed and in a dependent position.

TABLE IV

RECOVERY AFTER EXERCISE IN PERIPHERAL VASCULAR DISEASE

EXP.	O_2 CONTENT		CO_2 CONTENT		LACTIC ACID		O_2 CAPACITY	
	EXERCISE	REST	EXERCISE	REST	EXERCISE	REST	EXERCISE	REST
1	8.0	13.6	49.6	42.8	22.7	13.5	15.5	15.6
2	13.8	18.2	49.7	44.8	43.0	34.0	19.9	19.7
3	6.5	11.8	59.5	55.2	33.0	18.5	21.6	22.2
4	7.2	10.9	56.6	50.2	41.1	25.1	17.4	17.8
5	12.6	13.5	50.7	51.8	12.1	10.3	16.5	16.5
6	13.3	16.3	58.6	49.4	24.0	15.0		
7	13.3	20.1	63.8	51.9	19.7	14.6		
8	11.2	10.1	51.2	50.6	31.7	22.0		
9	9.0	9.9	61.5	57.3	52.5	36.5		
10	15.9	18.5	42.5	40.0	47.5	52.5		

The results (Table IV) parallel those in normal subjects who are recovering from fatigue. The oxygen deficit tends to disappear, and carbon dioxide and lactic acid values tend to return to their usual resting levels. There is, however, one important difference, namely, the time element. In many instances there were still an oxygen deficit and a high lactic acid level at the end of a test period of one-half, or even one hour, which is usually sufficient time for complete restitution in normal subjects. The inadequacy of the peripheral circulation was again demonstrated.

DISCUSSION

The fact that the arteriovenous anastomoses help to maintain the surface temperature of animals has been known for many years. Only recently did it become evident, through the studies of Grant and Bland[13] and Lewis and Pickering,[14] that they perform the same function in man.

The presence of active, contractile, comparatively large channels, which, like safety valves, permit rapid shifting or shunting of blood from the tissues directly into the venules is, of course, quite physiologic when the vascular tree is elastic and ample for tissue requirements; but in a region which has already been deprived of much of its vascular supply by disease processes, such a shunt can serve no useful purpose and may actually constitute a menace to the life of that part. Arterial blood laden with nutritive substances which are urgently needed by the tissues is sidetracked and returned to the general circulation without fulfilling its function.

Our experiments show that, at rest, the venous blood from a foot with impaired circulation carries more oxygen and frequently less carbon dioxide than the venous blood from the forearm. This is combined with a relatively high lactic acid content.

In the presence of peripheral vascular disease, the relatively high oxygen and low carbon dioxide values cannot be the result of increased

blood flow through the tissues. The constancy of the oxygen capacity shows that these abnormalities cannot be caused by an increase in blood concentration. They might be produced by a diminished permeability of the capillaries. However, we would then expect to find a low lactic acid concentration in the venous blood, and the capillaries should carry arterial blood throughout, i.e., the skin should have a bright red color.

We must therefore assume, as did Popoff, that, in peripheral vascular disease, patency of the arteriovenous anastomoses, even at rest, permits arteriovenous shunting of blood to play a major role in the peripheral circulation.

Under the influence of local muscular exercise, this shunting of blood is apparently reduced in many cases. Such patients respond to light exercise with utilization of blood oxygen and an accumulation of lactic acid. During the period of recovery, the local blood supply to the tissues was, in some instances, sufficient for a complete return to normal. In other cases, however, after the rest period, the venous blood still showed an oxygen deficit and a high lactic acid content. Occasionally, patency of the arteriovenous anastomoses was maintained during exercise, at a time when the demand for capillary circulation was very urgent. The "shunt" was manifested by an increase in oxygen content; insufficiency of the capillary circulation, by a marked accumulation of lactic acid.

It is apparent, therefore, that knowledge of the total blood flow through a given area, such as is obtained from plethysmographic studies, may be of little aid in estimating the efficiency of the local circulation. In certain cases only part of this blood passes through the capillaries and is available for utilization by the tissues. The remainder, which is shunted directly from arteriole to venule, is useful mainly in maintaining the local temperature. Although, according to Wright and Duryee,[15] there is some exchange of tissue fluid through the highly permeable venule walls, tissue metabolism depends essentially on capillary circulation. "Shunt" circulation, for practical purposes, is a loss as far as tissue metabolism is concerned.

This concept is important if we are to formulate a sound approach to the therapy of peripheral vascular disease. The ultimate purpose of all treatment must be improvement of the blood supply to the tissue proper.

SUMMARY

1. A relatively high oxygen and low carbon content of the venous blood from a region with impaired circulation, together with a relatively high lactic acid content, points to the presence of patent arteriovenous anastomoses.

2. Exercising an extremity in which the circulation is impaired produces either the usual chemical effect of fatigue, or, if a "shunt" circulation dominates, an increase in oxygen, together with an accumulation of lactic acid, in the venous blood.

3. The efficiency of the peripheral circulation in the presence of vascular disease of the extremities depends upon the flow of blood through the available capillary bed. Increased blood flow through an extremity when the arteriovenous anastomoses are patent does not necessarily mean that the capillary circulation to the tissues is augmented.

REFERENCES

1. Sucquet, J. P.: D'une circulation dérivative dans les membres et dans la tête chez l'homme, Paris, 1862.
2. Hoyer, H.: Ueber unmittelbare Einmuendung kleinster Arterien in Gefaessaeste venoesen Charakters, Arch. f. mikr. Anat. **13:** 603, 1877.
3. Grosser, O.: Ueber arterio-venoese Anastomosen an den Extremitaeten-Enden beim Menschen und den krallentragenden Saeugetieren, Arch. f. mikr. Anat. **60:** 191, 1902.
4. Miller, N., and Godfrey, J. S.: A Note on the Anastomosis of Arteries and Veins in a Cat, Anat. Rec. **13:** 177, 1917.
5. Brown, M. E.: The Occurrence of Arteriovenous Anastomoses in the Tongue of the Dog, Anat. Rec. **69:** 287, 1937.
6. Spanner, R.: Der Abkuerzungskreislauf der menschlichen Niere; Beitrag zur Kenntnis der Leistungszweiteilung ihres Gefaesssystems, Klin. Wchnschr. **2:** 1421, 1937.
7. Clark, E. R.: Arteriovenous Anastomoses, Physiol. Rev. **18:** 229, 1938.
8. Masson, P.: Les glomus neuro-vasculaires. Histophysiologie (Policard), Hermann et Cie, Paris, 1937.
   Les tumeurs glomiques souscoutanées en dehors des doigts, Ann. d' anat. path. **4:** 153, 1927.
9. Popoff, N. W.: The Digital Vascular System, Arch. Path. **18:** 295, 1934.
10. Goldschmidt, S., and Light, A. B.: A Comparison of the Gaseous Content of Blood From Veins of the Forearm and the Dorsal Surface of the Hand as Indicative of Blood Flow and Metabolic Differences in These Parts, Am. J. Physiol. **72:** 127, 1925.
11. Looney, J. M., and Childs, H. M.: A Comparison of the Methods for the Collection of Blood to Be Used in the Determination of Gases, J. Biol. Chem. **104:** 53, 1934.
12. Van Slyke, D., and Peters, J. F.: Quantitative Clinical Chemistry, Baltimore, 1932, Williams and Wilkins Co., Vol. II.
13. Grant, R. T., and Bland, E. F.: Observations on Arteriovenous Anastomoses in Human Skin and in the Bird's Foot With Special Reference to the Reaction to Cold, Heart **15:** 281, 1930.
14. Lewis, T., and Pickering, G. W.: Vasodilatation in the Limbs in Response to Warming the Body; With Evidence for Sympathetic Vasodilator Nerves in Man, Heart **16:** 33, 1931.
15. Wright, I. S., and Duryee, A. W.: Human Capillaries in Health and Disease, Arch. Int. Med. **52:** 545, 1933.

CARDIAC HYPERTROPHY CAUSED BY GLYCOGEN STORAGE DISEASE IN A FIFTEEN-YEAR-OLD BOY

WILLIAM ANTOPOL, M.D., ERNST P. BOAS, M.D., WILLIAM LEVISON, M.D., AND LESTER R. TUCHMAN, M.D.
NEW YORK, N. Y.

A CASE of abnormal glycogen deposition in a 15-year-old boy with extreme cardiomegaly was encountered. It differed somewhat from the classical cardiomegalic type of von Gierke's disease,[1-9] but, nevertheless, illustrated many of the cardinal features of this disorder of glycogen metabolism.

REPORT OF CASES

CASE 1.—*First admission*, Aug. 10, 1936; discharged, Aug. 28, 1936. A. H., a 15-year-old, Jewish schoolboy, entered the Mount Sinai Hospital because of progressively increasing dyspnea on exertion for the preceding two years. He had been "below par" for three years, as evidenced by his poor appetite, pallor, and fatigability. Three years before, he had experienced transient pain in his joints. Four years earlier, a teleoroentgenogram had shown a "bad heart."

Physical Examination.—The patient was a fairly well-developed and well-nourished white boy who was slightly dyspneic and orthopneic.

There was flatness to percussion at the extreme bases of both lungs posteriorly and in the axillae, with diminished intensity of the breath and voice sounds and absent fremitus. No râles were heard. The bases were not fixed.

The heart was markedly enlarged to the left. A short, blowing, systolic murmur was heard over the entire precordium. The rate was rapid and the beating was regular; gallop rhythm was audible over the entire precordium. The blood pressure was 120/80. The liver extended 1½ fingerbreadths below the costal margin, and was not tender.

Laboratory Examination.—The urine showed a trace of albumin on admission, but was negative thereafter. Acetone was tested for but not found. The hemoglobin was 100 per cent, the leucocyte count, 11,800, and the differential count, normal. The sedimentation time of the erythrocytes was four hours. The urea nitrogen content of the blood was 13 mg. per cent, the cholesterol content, 210 mg. per cent, the esterified cholesterol content, 65 mg. per cent, and the sugar content, 105 mg. per cent. The icteric index was 16. The blood Wassermann reaction was negative. The electrocardiogram revealed sinus tachycardia and an atypical, left-sided, bundle branch block.

Roentgenologic examination of the chest revealed a generalized enlargement of the heart, particularly of the left ventricle, which was both hypertrophied and dilated. There was enlargement of the left auricle, with elevation of the left main bronchus, giving the appearance of a combined mitral and aortic lesion. Slight pulmonary congestion was evident.

From the Medical Service of Dr. George Baehr and the Pathological Laboratories of Mount Sinai Hospital, New York, and the Pathological Laboratories of the Newark Beth Israel Hospital, Newark, N. J.

Received for publication May 1, 1939.

Course and Diagnosis.—The congestive heart failure was quickly relieved by rest in bed, mercupurin, and digitalis. The gallop rhythm also disappeared. The cause of the hypertrophy remained obscure. Congenital heart disease was eliminated because of the absence of characteristic murmurs, cyanosis, and confirmatory roentgenologic observations. The fact that there was no definite history of rheumatic fever, together with the absence of characteristic murmurs, made it unlikely that this was a case of rheumatic valvulitis. Two other possible causes of the hypertrophy, namely, chronic interstitial myocarditis (Fiedler's myocarditis) and von Gierke's disease, were considered. In the absence of hypoglycemia and acetonuria and of excessive enlargement of the liver and kidneys beyond that which might be expected in cardiac insufficiency, and because of the age of the patient, the possibility of von Gierke's disease was clinically ruled out. In view of all of the above considerations, a diagnosis of cardiac hypertrophy of unknown cause was made.

Second admission, Oct. 1, 1936; died, Nov. 7, 1936. After his discharge from the hospital, the patient had been free from all symptoms, except dyspnea on exertion, until one week before readmission, when he felt feverish and coughed up small amounts of non-foul-smelling sputum. Following this, he developed fever and a persistent cough, and occasionally vomited.

Physical examination revealed essentially the same abnormalities as on the first admission. The arterial pressure measured 140/92 mm. Hg, and the venous pressure, 15 cm. of water. There was slight pretibial edema.

The results of the laboratory examination did not vary from those on the first admission, except that the fasting blood sugar content was 70 mg. per cent, the cholesterol content, 155 mg. per cent, and the esterified cholesterol content, only a trace. The electrocardiogram was essentially the same as on the first admission.

During the patient's stay in the hospital he had a persistent fever of 101° which was attributed to chronic sinusitis. The blood culture remained sterile. Four weeks after admission the spleen became palpable. Because of this and the fever, the possibility of active myocarditis was entertained. The vital capacity was diminished to 1900 c.c. The saccharin circulation time was prolonged to forty-five seconds. Five and one-half weeks after admission there was an increasing degree of congestive heart failure, and the patient died in his sleep.

Necropsy.—(10127.) Necropsy was performed twelve hours after death.

The body was that of a well-developed white boy, 15 years of age, in complete rigor mortis. There was edema of the ankles.

Abdomen.—The peritoneal cavity contained a small quantity of turbid fluid. The mesentery was edematous. The liver extended 4 cm. below the costal margin in the midclavicular line. The spleen did not project beyond the costal margin.

Thorax.—The heart was universally enlarged (Fig. 1), and, together with the root of the aorta, weighed 650 grams (average normal, 247.5). Chemical studies revealed that the glycogen content of the heart muscle was 4 per cent, despite the fact thai the necropsy was performed twelve hours after death. The heart displaced both lungs in such a way that each was compressed into the lateral and posterior hemithorax, particularly on the left side. The pleurol cavities were normal. The right auricular appendage was dilated. The atrium had a distinctly thickened wall, and the endocardium was opaque. The foramen ovale was closed. The septal leaflet of the tricuspid valve was slightly thickened. The right ventricular wall was 1 cm. thick. The septal portion bulged into this ventricular chamber, narrowing the cavity. The endocardium was translucent. The underlying myocardium had a homogeneous, pale, yellow-brown color. The outflow tract of the right ventricle was markedly hypertrophied, and bulged into the ventricular lumen. The pulmonary cusps showed no significant changes. The width of the pulmonary artery just above the free margin of the cusps was 7.5 c.mm. (average normal, 5.9).[10] The

pulmonary artery showed nothing unusual. The endocardium of the left auricle was uniformly thickened and opaque, and, in places, finely wrinkled. There was no evidence of a MacCallum lesion. There was a fine, ridgelike thickening along a short area of the free margin of the posterior leaflet of the mitral valve, together with slight, irregular thickening of a few chordae tendineae. No vessels could be detected in the valve. The left ventricular wall was considerably thickened; it measured 1.8 cm. in its midportion. On section, the musculature was reddish gray. The chamber was elongated and markedly dilated. The endocardium was irregularly thickened, grayish, and opaque, especially in the outflow tract. There were no regurgitation pockets. Irregularly distributed areas of purple coloration were seen in the anterior papillary muscle, the posterior wall of the ventricle, and the upper, anterior portion of the interventricular septum. The aortic cusps showed no significant changes. The commissure between the posterior and left anterior cusps was slightly fused. The coronary vessels were patent throughout their course. The aortic valve measured 5.1 cm. across (average normal, 5.42).

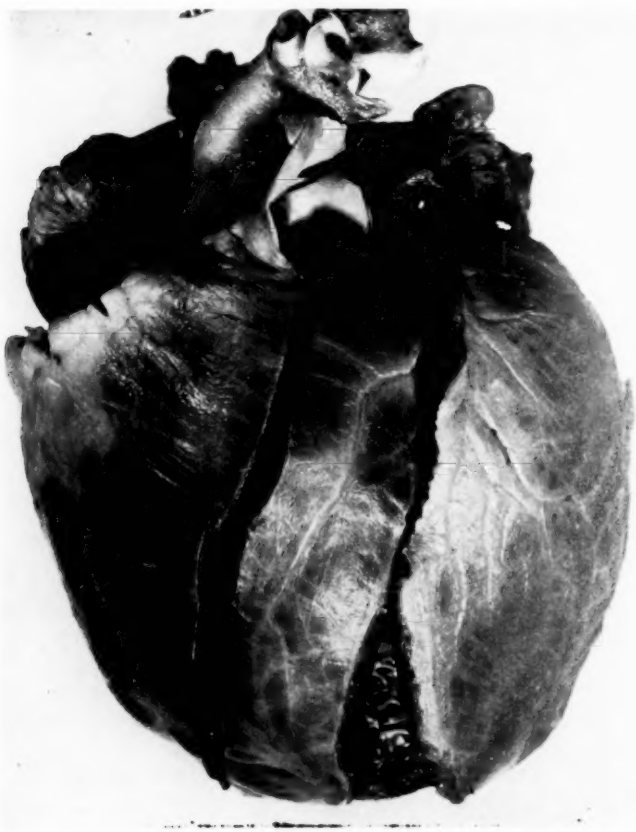


Fig. 1.—Heart showing hypertrophy of the left and right ventricles.

The circumference of the aorta at the beginning of the descending thoracic portion was 4.2 cm. (normal, 4.3), and, at the branching of the coeliac axis, 3.5 cm. (normal 3.84 at diaphragm). The aorta was elastic. The intima was smooth except for a few, small, slightly raised, yellow plaques in the descending thoracic portion.

Lungs.—The lungs were markedly congested. There were small hemorrhagic infarcts in the right upper and left lower lobes. On the left there was a middle lobe whose shape and bronchial supply corresponded to those of the right middle lobe. The pulmonary vessels were not unusual.

Liver.—The liver weighed 1850 grams. It was firm, large, and had a rounded edge. The surface was smooth and deep purple. The cut surface had a distinct brown appearance. The architecture was well discernible. The central zones of the lobules were seen as fine, red dots and streaks. The hepatic vessels and portal vein showed no gross abnormalities.

Spleen.—The spleen was very firm and congested, and weighed 470 grams. The follicles were large and prominent.

Kidneys.—The kidneys were red-brown and firm, and, together, weighed 380 grams. No gross changes were observed.

Lymph Nodes.—The intra-abdominal and intrathoracic lymph nodes were slightly enlarged and moderately firm.

Sections of all organs were fixed in absolute alcohol and formalin for histologic study. The weighed portions were minced and placed in acetone, alcohol, and glycerine for chemical studies.

Histologic Changes.—Heart: The most conspicuous changes were found in the left ventricular myocardium. The right ventricle was similarly involved, but to a lesser extent. With the hematoxylin and eosin stain, in paraffin sections, most of the muscle fibers were found to contain an elongated, irregularly outlined, elliptical area which was either empty or filled with a very delicate basophilic or slightly eosinophilic network. In places, the vacuoles in the central zones of the muscle fiber were so pronounced that only a thin, cylindrical shell of muscle substance (sarcoplasm) could be seen on cross section. Many of these vacuolated zones also contained clumps of a homogeneous, darkly basophilic material. This has been described in only one other instance of von Gierke's disease.[9] The nuclei were mostly very large, and presented bizarre, angulated, or elongated forms, with dense, basophilic, clumped, chromatin material. Their situation within the individual fibers was variable. In places, the nuclei were found in the center of the vacuole, and were completely surrounded by it, but, for the most part, they were situated in the periphery of the vacuole, as though pushed aside (Fig. 2*A*). In scattered areas of the left ventricular wall there was a moderate proliferation of fibroblasts, and some fibers were surrounded by small collections of round cells (Fig. 2*B*), with occasional histiocytes and polymorphonuclear leucocytes. Scattered throughout the myocardium there were also foci of interstitial fibrosis (Fig. 2*D*); these were not confined to the perivascular zones.

In one place there was a marked, fibrous thickening of the wall of a small vein, which contained an organizing parietal thrombus. The small arteries showed no significant changes. The mediae of the larger arteries were moderately thickened as the result of the deposition of a homogeneous substance between the muscle bundles, but only a very few of the muscle fibers stained red with Best's carmine. The auricular endocardium was slightly thickened. There was moderate subendocardial fibrosis, with an increase in fibroblasts. The auricle was otherwise normal. The mitral valve showed slight fibrous thickening. No vessels were seen in the valve. The aortic and tricuspid valves showed no significant histologic changes. The ventricular endocardium was slightly thickened.

Sections of myocardium which were stained with Best's carmine showed large amounts of glycogen not only in the zones where vacuoles were seen in the hematoxylin-eosin preparations, but also in the intracellular basophilic bodies described above. The glycogen in the inner zones of the muscle fibers was deposited

homogeneously, and only under high magnification could one occasionally distinguish fine droplets. The endomysial cells were easily discernible. Rarely, an endomysial cell was slightly swollen, and contained small amounts of homogeneously stained glycogen.

In some places, the cross striations appeared as straight lines impregnated with glycogen; in others, the glycogen was strung along the cross striations in red droplets, like beads on a thread. This corresponds to the distribution of glycogen in control sections from comparatively normal hearts.

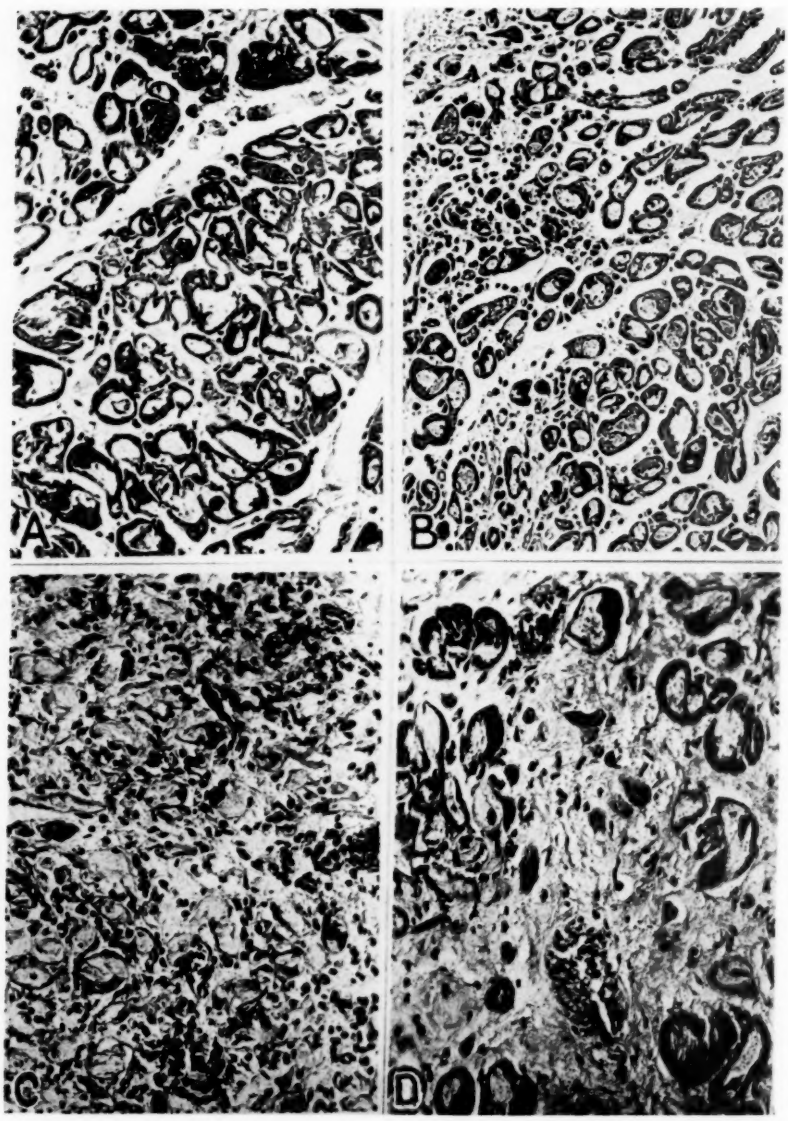


Fig. 2.—Hematoxylin and eosin stain of, *A*, vacuolated myocardial fibers. Some of the nuclei are compressed. *B*, Vacuolated myocardial fibers. Interstitial collections of round cells. *C*, Degenerated and necrotic myocardial fibers with inflammatory reaction. *D*, Myocardium with areas of fibrosis. (×175.)

Interventricular Septum.—The general appearance was similar to that of the left ventricular wall, except that the inflammatory lesion was more severe. A broad area beneath the left ventricular endocardium, particularly in the uppermost portion, was the seat of very conspicuous infiltration. In large, irregularly outlined areas, the myocardium was replaced by a highly vascularized, and in places, hyalinized, connective tissue. In its meshes were fragments of degenerating muscle fibers, with indistinct striations, which retained their large, pyknotic nuclei. Most of the fibers were filled with glycogen, so that only a very thin mantle of sarcoplasm remained about the masses which contained basophilic glycogen. About these degenerating muscle fibers there was a severe inflammatory reaction, with numerous, large histiocytes, lymphocytes, and scattered polymorphonuclear leucocytes (Fig. 2*C*). No plasma cells were noted. In many instances the inflammatory cells surrounded, and appeared to be attacking, single, degenerating muscle fibers. Free masses of glycogen were also found. Large numbers of phagocytes were laden with glycogen. In areas of very dense cellular infiltration, the proportion of polymorphonuclear leucocytes was greater than in the remaining tissue.

We failed, as did Putschar,[2] Humphreys and Kato,[8] and Wolff,[9] to differentiate histologically the fibers of the conduction system from the remainder of the glycogen-laden heart muscle fibers, although serial sections were studied in the region of the bundle of His. Histologic examination of the bundle region showed an extensive inflammatory reaction. The electrocardiogram in this case revealed bundle branch block, indicating an involvement of the conduction system.

Peripheral Muscle (Psoas).—The muscle fibers were very broad, and showed many central vacuoles and masses. These also gave a positive glycogen reaction. The nuclei were in their normal peripheral position. The sarcolemma cells were swollen, and contained considerable amounts of glycogen; thus, the sarcolemma formed a peripheral coat around the muscle fiber (Fig. 3*B*). In many places the granular deposits in the fibers were so massive that only scattered fragments of fibers and a mantle of endomysium remained. The degenerated muscle fibers were surrounded by round cells, histiocytes, and, occasionally, polymorphonuclear leucocytes (Fig. 3*A*). A great number of glycogen-containing phagocytes were noted within the endomysium. The phagocytic action of these cells has been stressed by Maximow and Bloom.[30]

Muscle From the Neck.—The fibers were normal, and there were small amounts of glycogen. In only a few fibers was the glycogen centrally located.

Tongue.—The musculature did not show any significant changes. In a few areas, muscle fibers were surrounded by thin sheaths of glycogen which, apparently, was deposited in sarcolemma cells.

Diaphragm.—The glycogen deposition was similar to that in the psoas muscle, but there was much less of it.

Esophagus.—The striated muscle fibrils did not take the glycogen stain. In the smooth muscle, however, there were numerous fibers which contained homogeneous masses of glycogen; in some places these were basophilic.

Smooth Muscle.—Examination of the smooth musculature throughout the body showed that there was a considerable amount of homogeneous glycogen in single muscle fibers. It was basophilic in many places. Large deposits were noted in the fibers of the *bronchial musculature* and in the muscle of the *epididymis.* Moderate amounts were present in the musculature of the *bladder, prostate,* and many *arteries* and *veins.* This was demonstrated in the carotid artery, vessels of the adrenal, and arteries and veins in the lungs, gall bladder, and epididymis. In hematoxylin-eosin preparations, the areas corresponding to the glycogen were often basophilic.

Liver.—There was marked chronic passive congestion. The central liver cells contained large amounts of lipofuscin and fat. There were marked congestion and edema in the Desse spaces. The Kupffer cells were not prominent. The portal fields showed moderate infiltration with round cells and a few polymorphonuclear leucocytes. The hematoxylin-eosin stain showed that numerous liver cells had a pale, eosinophilic, foamy cytoplasm and a basophilic rim. The nucleus was displaced to the periphery. Best's carmine stained these cells intensely red; the remainder of the liver cells showed glycogen granules only along their borders. In general, there was a fairly large amount of glycogen, but this did not exceed the amounts found histologically in some control slides. The deposited glycogen granules, however, appeared coarser than those in the control livers.

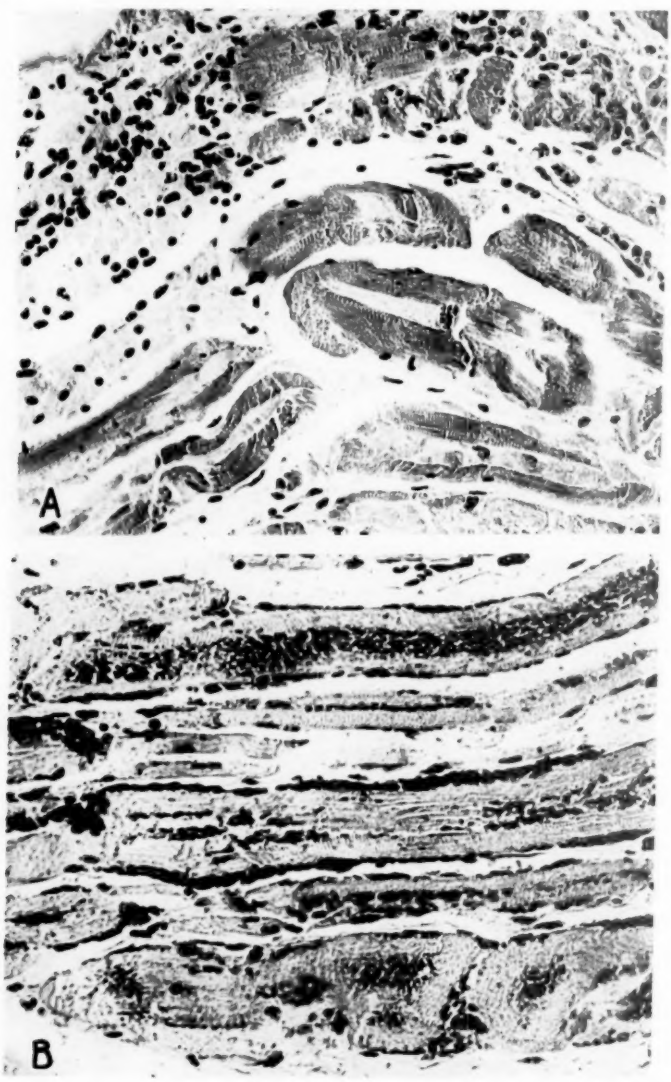


Fig. 3.—*A*, Hematoxylin and eosin stain. Psoas muscle with basophilic masses in fibers and interstitial collections of round cells. *B*, Best carmine stain. Glycogen in sarcolemma and in muscle fibers. (×258.)

Lungs.—The histologic changes were those of chronic passive congestion. A section from the left lower lobe showed an organizing arterial embolus and hemorrhagic infarction.

Spleen.—Sinus hyperplasia was prominent. The follicles were well outlined.

Kidney.—There was marked congestion. Bowman's spaces contained coagulated plasma and a few erythrocytes. The tubules were degenerated, and contained very small amounts of fat. No glycogen was found within the renal epithelium.

Stomach and Intestinal Tract.—There were only sporadic glycogen-containing muscle fibrils. The pyloric musculature was free from glycogen.

Sections of the thyroid, lymph nodes, bone marrow, peripheral nerves, sympathetic ganglia, adrenals, brain, pituitary, and pancreas showed no significant changes.

Inasmuch as von Gierke's disease has been reported in siblings,[31, 33, 34] the case of A. H.'s 11-year-old brother, which was very similar, is also presented.

CASE 2.—This boy was admitted to the Mount Sinai Hospital March 31, 1937, with a complaint of shortness of breath and pallor of five weeks' duration. One brother (A. H., Case 1) had died at the Mount Sinai Hospital, four months earlier, of glycogen storage disease which chiefly involved the heart muscle; one other brother was living and well. The patient had always tended to be obese, and had been on a reducing diet several times.

His illness had probably started several months before admission, at which time he complained of shortness of breath and palpitation on climbing stairs. Five weeks before admission, the patient had an upper respiratory infection, with a temperature of 101 to 102° F. His mother stated that he was uncomfortable, and that his respirations were rapid when he was in the recumbent position. The dyspnea increased rapidly, and immediate hospitalization was advised because he was thought to have "pericarditis." At another hospital he was given oxygen through an intranasal catheter for three days, which relieved his dyspnea somewhat. After one week in the hospital, the patient was taken home against advice. In the week preceding his admission to the Mount Sinai Hospital, the anorexia, nausea, vomiting, dyspnea, and orthopnea continued. It was noted that the legs had become swollen in the dependent portions. The urinary output had diminished. On the day of admission the patient was irrational and delirious.

Physical Examination.—The temperature was 98.8° F., the pulse rate, 112, and the respiratory rate, 34. The patient appeared to be both acutely and chronically ill; he was pale, looked tired, and had moderate dyspnea and orthopnea. The skin was cool, dry, and rough. The precordium bulged slightly. There were dullness to percussion and diminished intensity of the breath sounds at the base of the right lung. The point of maximum impulse was felt in the fifth intercostal space in the anterior axillary line; percussion showed that the heart was enlarged to the right and left; the left border was near the anterior axillary line. The heart rate was rapid and the sounds were faint; the pulmonic second sound was louder than the aortic, and there was a moderately loud systolic murmur over the apex which was transmitted upward and outward. The systolic blood pressure was 90; the diastolic could not be measured. The liver was palpable 6 cm. below the costal margin in the midclavicular line. Both flanks bulged slightly.

It was our impression, on admission, that the patient had von Gierke's disease, with myocardial failure. A teleoroentgenogram showed marked enlargement of the heart to the left and right.

Laboratory Examination.—The urea nitrogen content of the blood was 10 mg. per cent. The Janney test gave the following result: 70, 85, 115, 110, and 95. The

chloride content of the blood was 510 mg. per cent, the phosphorus content, 3.75 mg. per cent, and the calcium content, 7.8 mg. per cent. The Takata-Ara test was negative. The blood Wassermann reaction was negative. The icteric index was 12. The galactose tolerance test was negative. The total protein content of the plasma was 5.7 per cent, of which albumin was 2.9, and globulin, 2.8. The cholesterol content of the blood was 185 mg. per cent, and the esterified cholesterol content, 36 mg. per cent.

The hemoglobin was 96 per cent, the erythrocyte count, 4,190,000, the leucocyte count, 22,600, and the platelet count, 195,000. The differential leucocyte count showed 83 per cent polymorphonuclears, 7 per cent juvenile cells, 9 per cent lymphocytes, and 1 per cent monocytes. Examination of the blood smear showed anisocytosis, polychromatophilia, and giant platelets. The tourniquet test was negative.

The urine was normal on several occasions, but the last specimen which was examined contained a few hyaline and granular casts; acetone was found in the urine only once while the patient was vomiting.

The electrocardiogram revealed sinus tachycardia and changes which were interpreted as indicative of left ventricular enlargement, myocardial disease, and left bundle branch block.

Course.—The patient grew progressively worse. He was afebrile on admission, but thereafter he had a low-grade fever which exceeded 100° F. on two days only. He died with the clinical manifestations of myocardial failure. Permission to perform an autopsy could not be obtained.

DISCUSSION

The outstanding features of the first case were the excessive deposits of glycogen in the heart and systemic musculature and the pronounced cardiac hypertrophy.

We believe that the patient had the cardiomegalic type of von Gierke's disease. However, because of his age, a critical consideration of other possibilities is in order, for, of the cases so far reported, none has occurred in patients beyond the age of 8 months, except possibly in the case of Fliess and Bloom, in which the patient was still alive at the age of 2 years and 4 months.[11]

The changes in certain areas of the heart muscle resembled those which are caused by coronary occlusion. It is known that, after severe myocardial ischemia, the vacuoles, as a rule, contain glycogen. The patency of the coronary arteries, the normal dimensions of the main vessels, and the absence of congenital defects exclude the possibility that mechanical interference with the blood supply was a factor in this case. It might, however, explain the localized glycogen deposition in the case of Finkelstein,[12, 20] in which the left coronary artery arose from the pulmonary artery.

The vacuolated myocardial fibers in cases of beriberi[13] simulate those which were found in the present case.[14, 15]

This case also throws further light on the relationship between some cases of idiopathic hypertrophy of the heart and von Gierke's disease.[2, 4, 5, 7, 8] The term "idiopathic hypertrophy of the heart" is used when no cause for the hypertrophy can be found.[18, 19] The cardio-

megalic form of von Gierke's disease was placed in a separate category as soon as its true nature had been established.[21] Although the existence of other etiologic factors in "idiopathic hypertrophy" cannot be denied, glycogenosis may also play a significant role in the causation of cardiac hypertrophy of obscure pathogenesis. "Idiopathic hypertrophy of the heart" occurs not only in early infancy, but also in later childhood.[18, 19, 22, 23, 24] If the cardiac manifestations of abnormalities of glycogen metabolism should be related to some of the instances of idiopathic hypertrophy, they also should occur after infancy. The arrest of glycogen storage disease without cardiac involvement has been reported in older children,[2, 5, 25, 26, 27, 29, 32] and, in some of the cases in which no cardiac enlargement was found clinically, post-mortem examination revealed the presence of large amounts of glycogen within the heart.[1, 3, 16]

It is also to be considered that, in contrast to the liver, the overfilling of the myocardium with glycogen is distinctly abnormal after infancy, and it is questionable whether, after a prolonged period of engorgement with glycogen, the myocardium can return completely to its normal functional and morphologic state. In addition, the inflammatory response to these severe, irreversible, degenerative changes, together with necrosis of the myocardium, might further hinder recuperation. The eventual, composite picture would consist, therefore, of normal areas, areas in which the myocardial fibers harbored an abundance of glycogen, areas of inflammation (Fig. 2*B* and *C*), and areas of fibrosis (Fig. 2*D*). This pattern was found in our case and has also been described in some of the cases of idiopathic hypertrophy of the heart.

SUMMARY

Evidence is presented which suggests that some cases of idiopathic hypertrophy of the heart, described in the older literature, represent end stages of glycogenosis of the heart, and that our first case represents a transition between the infantile, fully developed picture of massive glycogen deposition, and the end stage, with only reactive inflammation, degeneration, and fibrosis.

REFERENCES

1. von Gierke, F.: Hepato-Nephromegalia Glykogenica, Beitr. z. path. Anat. u. z. allg. Path. **82**: 497, 1929.
2. Putschar, W.: Über angeborene Glykogen-Speicherkrankheit des Herzens, "Thesaurismosis Glykogenica," Beitr. z. path. Anat. u. z. allg. Path. **90**: 222, 1932.
3. Bischoff, G.: Zum klinischen Bild der Glykogen-Speicherungskrankheit (Glykogenose), Ztschr. f. Kinderheilk. **52**: 722, 1932.
4. Pompé, S. C.: Hypertrophie idiopathique du coeur, Annales d'anatomie et pathol. **10**: 23, 1933.
5. van Creveld, S.: Über die Rolle des Glykogens bei der Enstehung von Organvergrösserungen, Klin. Wchnschr. **12**: 529, 1933.
6. Ellis, R. W. B.: Congenital Hypertrophy of Heart? (Cardio-megalia glycogenica specimen) Proc. Roy. Soc. Med. **28**: 1330, 1935.

7. Antopol, W., Heilbrunn, J., and Tuchman, L.: Enlargement of Heart Due to Glycogen Storage in von Gierke's Disease, Am. J. M. Sc. **188:** 354, 1934.
8. Humphreys, E. M., and Kato, K.: Glycogen Storage Disease; Thesaurismosis Glycogenica (von Gierke), Am. J. Pathol. **10:** 589, 1934.
9. Wolff, K.: Beitrag zur Morphologie und Chemie der Glykogenspeicherkrankheit, Beitr. z. path. Anat. u. z. allg. Path. **97:** 289, 1936.
10. Roessle, R., and Roulet, F.: Mass und Zahl in der Pathologie, 1932, Julius Springer (For all normal figures).
11. Fliess, M. M., and Bloom, S. M.: von Gierke's Glycogen Storage Disease; Case Report With Unusual Findings, J. Pediat. **12:** 635, 1938.
12. Finkelstein, L. E.: Cardiomegalia Glycogenica Circumscripta, Am. J. M. Sc. **191:** 415, 1936.
13. Wenckebach, K. F.: Das Beri-Beri Herz, Berlin, 1934, Julius Springer.
14. Antopol, W.: Practitioner's Library of Medicine and Surgery **13:** 253, Chapt. XXXII, 1937.
15. Klemperer, P.: Cardiovascular Lesions in Avitaminoses, J. Mt. Sinai Hosp. New York **4:** 966, 1938.
16. Unshelm, E.: Über die Glykogenkrankheit, Deutsche. med. Wchnschr. **60:** 633, 1934.
17. Kimmelstiel, P.: Über Glykogenose, Beitr. z. Anat. u. z. allg. Path. **91:** 1, 1933.
18. Stoloff, E. G.: So-Called Idiopathic Enlargement of Heart in Infancy and Childhood, Am. J. Dis. Child. **36:** 1204, 1928.
19. Kugel, M. A., and Stoloff, E. G.: Dilatation and Hypertrophy of Heart in Infants and Young Children, With Myocardial Degeneration and Fibrosis (So-Called Congenital Idiopathic Hypertrophy), Am. J. Dis. Child. **45:** 828, 1933.
20. Carrington, G. L., and Krumbhaar, E. B.: So-Called Idiopathic Cardiac Hypertrophy in Infancy, Am. J. Dis. Child. **27:** 449, 1924.
21. Sprague, H. B., Bland, E. F., and White, P. D.: Congenital Idiopathic Hypertrophy of Heart; Case With Unusual Family History, Am. J. Dis. Child. **41:** 877, 1931.
22. Michaud, L.: Beitrag zur Kenntnis der kongenitalen idiopathischen Herzhypertrophie, Cor. Bl.f. Schweiz. Aerzte. **36:** 779, 1906.
23. Howland, J.: Idiopathic Hypertrophy of the Heart in Young Children, Contributions Medical and Biological Research, New York **1:** 584, 1919, Paul B. Hoeber, Inc.
24. Cathala, J.: Sur un syndrome de Myo-hypertrophie cardiaque primitive, Bull. et mém. Soc. méd. d. hôp. de Paris **50:** 1795, 1926.
25. Ellis, R. W. B.: Hepatomegaly in Infant (Hepatomegalia Glycogenica? Hypertrophic Steatosis), Proc. Roy. Soc. Med. **28:** 833, 1935.
26. Anderson, P. M.: Glycogen Accumulation Disease, M. J. Australia **1:** 362, 1935.
27. Naish, A. E.: von Gierke's Disease Associated With Amylorrhea, Brit. Med. J. **1:** 360, 1936.
28. Lindsay, L. M., Ross, A., and Higglesworth, F. W.: von Gierke's Glycogen Disease, Ann. Int. Med. **9:** 274, 1935.
29. Worster-Drought, E., and Parkes Weber, F.: Hepatomegaly With Persistent Ketonuria in Child; Probably Case of von Gierke's "Glycogen Accumulation Disease," With Functional Recovery, Brit. M. J. **1:** 403, 1933.
30. Maximow, A. A., and Bloom, W.: A Textbook of Histology, Ed. 2, 1935, p. 153.
31. Beumer, H.: Zum Stoffwechsel und zur Differentialdiagnose der Glykogenspeicherkrankheit, Neue Deutsche Klinik, Erg. Bd. **1:** 327, 1933.
32. Zelson, C., and Rauh, L.: Disturbance in Glycogen Metabolism With Hepatomegaly (von Gierke's Disease), Am. J. Dis. Child. **47:** 808, 1934.
33. Moolten, S.: Personal Communication.
34. Willis, R. W. B.: Hepatomegalia Glycogenica (von Gierke's Disease). Associated With Infantilism in Three Siblings, Proc. Roy. Soc. Med. **28:** 1180, 1935.

THE SIMULTANEOUS ACTION OF CERTAIN DRUGS ON THE BLOOD PRESSURE AND ON THE FLOW IN THE RIGHT AND LEFT CORONARY ARTERIES

R. Wégria, M.D.,* Hiram E. Essex, Ph.D., J. F. Herrick, Ph.D., and Frank C. Mann, M.D.
Rochester, Minn.

In a previous paper,[1] the influence of certain drugs on the blood flow in the right and left coronary arteries of the trained dog was reported. Two series of experiments were done; in one, the flow in the right coronary artery was studied, and, in the other, the flow in the left coronary artery. Although the results obtained on the trained dog had clearly indicated a similarity in the response of the flow in the two coronary arteries to these drugs, simultaneous observations on the blood flow in these vessels and a knowledge of the behavior of the arterial blood pressure during the experiments were considered desirable. Such relatively extensive procedures were believed to be excessive for the trained dog. However, it proved feasible to observe simultaneously the action of drugs on the coronary arteries and the blood pressure of the anesthetized dog. The recognized disadvantages of using an anesthetic (chloralosane) were offset by the advantage of being able to obtain more complete information with respect to the action of each of the drugs used. In addition, it would be possible to evaluate the influence of anesthesia on coronary flow by comparing the results of such experiments with the data already obtained on the trained animal. For these and other reasons, experiments were done with the following ten drugs: amyl nitrite, nitroglycerin, theophyllin-ethylenediamine (aminophyllin), histamine acid phosphate, acetyl-β-methylcholine chloride (mecholyl), papaverine, epinephrine, pitressin, pyridine-β-carbonic acid diethylamide (coramine), and atropine sulfate.

METHOD

The thermostromuhr method was used, as in previous experiments reported from this laboratory.[2, 3]

Dogs which weighed from 15 to 38 kg. were used. Under chloralosane anesthesia and artificial respiration, the two units were applied. On the left side, the chest was opened through the fifth intercostal space, and, after incising the pericardium, and after the necessary dissection, a thermostromuhr unit of proper caliber was applied to the circumflex branch of the left coronary artery as near its origin as was practicable. The pericardium and chest were then closed in the usual manner. The right coronary artery was approached in the same manner, through the fourth intercostal space on the right side of the chest, and a thermostromuhr unit was

Division of Experimental Medicine, The Mayo Foundation, Rochester.
Received for publication Feb. 18, 1940.
*Fellow of the Belgian-American Educational Foundation.

TABLE I

THE SIMULTANEOUS EFFECT OF CERTAIN DRUGS ON BLOOD FLOW IN THE CIRCUMFLEX BRANCH OF THE LEFT CORONARY ARTERY AND THE RIGHT CORONARY ARTERY (CHLORALOSANE ANESTHESIA)

DOG WEIGHT, KG.	DRUG AND DOSE	CONTROL FLOW, C.C. PER MINUTE	MAXIMAL FLOW, C.C. PER MINUTE	PERCENTAGE INCREASE OR DECREASE	COMMENT
35	Amyl nitrite	L 80	115	+44	Returned to control level after 1 min.; followed by a decrease of 21 per cent, lasting more than 7 min.
	inhalation	R 21.5	37	+72	Returned to control level after 1.5 min.; followed by a decrease of 15 per cent, lasting more than 7 min.
38	Nitroglycerin 1.3 mg.	L 180	600	+233	Returned to control level after 4 min.; no subsequent decrease.
		R 83	178	+114	Returned to control level after 2 min.; followed by a decrease of 25 per cent for more than 4 min.
22	Nitroglycerin 1.3 mg.	L 116	150	+29	Returned to control level after 1 min.; followed by decrease of 14 per cent for 1.5 min.
		R 77	122.5	+59	Returned to control level after 1.5 min.; followed by a decrease of 12 per cent for more than 3 min.
35	Nitroglycerin 0.65 mg.	L 67	116	+73	Returned to control level after 2 min.; no significant decrease.
		R 21	37	+76	Returned to control level after 1 min.; followed by a decrease of 29 per cent for 5 min.
35	Aminophyllin 0.24 Gm.	L 85	310	+265	Had not returned to control level after 14 min.
		R 24	56	+133	
22	Aminophillin 0.24 Gm.	L 120	182	+52	Had not returned to control level after 9 min.
		R 64	106	+66	
38	Histamine acid phosphate 0.5 mg.	L 145	500	+245	Returned to control level after 3 min.; followed by decrease of 20 per cent for more than 3 min.
		R 59	284	+381	Returned to control level after 2.5 min.; followed by decrease of 37 per cent for more than 3 min.
18.4	Histamine acid phosphate 0.25 mg.	L 126	300	+138	Returned to control level after 5 min. No decrease.
		R 61	258	+323	Had not returned to control level after 11 min. No further decrease.
22	Histamine acid phosphate 0.5 mg.	L 114	170	+49	Returned to control level after 1 min. No significant decrease.
		R 66	130	+97	Returned to control level after 1.5 min. No significant decrease.
15.7	Papaverine 20 mg.	L 40	80	+100	Returned to control level after 7 min. No significant decrease.
		R 23	44	+91	Returned to control level after 2.5 min. No significant decrease.

TABLE I—CONT'D

DOG WEIGHT, KG.	DRUG AND DOSE	CONTROL FLOW, C.C. PER MINUTE	MAXIMAL FLOW, C.C. PER MINUTE	PERCENTAGE INCREASE OR DECREASE	COMMENT
20	Papaverine 20 mg.	L 108	146	+35	Returned to control level after 4 min. No decrease.
		R 20	29	+45	Had not returned to control level after 6 min. No decrease.
35	Epinephrine 0.05 mg.	L 45	113	+151	Had not returned to control level after 9 min. No decrease.
		R 13.5	25	+85	Returned to control level after 3 min. No decrease.
22	Epinephrine 0.05 mg.	L 124	215	+73	Returned to control level after 2 min.
		R 67.5	114	+69	Returned to control level after 2.5 min.
35	Epinephrine 0.05 mg.	L 78	200	+156	Returned to control level after 2 min. No significant decrease.
		R 26	60	+131	Returned to control level after 2 min. No significant decrease.
15	Epinephrine 0.025 mg.	L 70	194	+177	Had not returned to control level after 9 min.
		R 34.5	113.5	+229	Had not returned to control level after 9 min.
22	Pitressin 2 pressor units	L 132	85	−36	Had not returned to control level after 19 min.
		R 76	15	−80	Had not returned to control level after 19 min.
19	Pitressin 0.5 pressor unit	L 63	35	−44	Returned to control level after 9 min.
		R 15	less than 10	−	Had not returned to control level after 14 min.
22	Coramine 250 mg.	L 126	142	+13	Returned to control level after 2 min. No significant decrease.
		R 69	81	+17	
15.7	Atropine sulfate 2 mg.	L 35	47	+34	Still maximally increased 23 min. after the injection.
		R 22	31	+41	

applied to that vessel near its origin. The pericardium and chest were then closed, and normal respiration was restored. In a few instances, however, the chest was left open and artificial respiration was maintained throughout the experiment. The left femoral artery was cannulated, and the mean arterial blood pressure was recorded optically. The right femoral vein was exposed for the injection of drugs, all of which, with the exception of amyl nitrite, were given intravenously.

RESULTS

To conserve space only one reaction to each drug will be described; the essential data on a number of representative experiments are recorded in Table I. Much of the literature which is concerned primarily with the effect on coronary flow of the drugs under consideration was dealt with in our previous paper.[1] For the sake of brevity, many pertinent references have been omitted in this report.

1. *Amyl nitrite.*—A dog which weighed 38 kg., with a mean blood flow of 180 c.c. per minute in the circumflex branch of the left coronary artery and 115 c.c. per minute in the right coronary artery, had a mean

blood pressure of 137 mm. of mercury and a heart rate of 133 beats per minute. The contents of one ampule (0.33 c.c.) of amyl nitrite were given by inhalation through an intratracheal tube for four minutes. Ten seconds after the beginning of the inhalation, the blood flow in both coronary arteries increased; the maximal flow was 511 c.c. per minute in the circumflex branch and 398 c.c. per minute in the right coronary artery. These maximal increases were reached within one minute, and, although the administration of amyl nitrite was continued for four minutes, the blood flow in the circumflex branch had returned to its control level within three minutes, and, in the right coronary artery, within six minutes. The blood pressure decreased to 130 mm. of mercury and returned to its control value after seven minutes. The heart rate, after an increase to 180, returned to the control level after two minutes and thirty seconds. The reactions to amyl nitrite were not always the same as the one described. In some cases the fall in blood pressure was greater and more prolonged; the heart rate sometimes remained increased after the blood flow had returned to its control value. Generally, the blood flow returned rapidly to the control level, but, in one experiment, the increase in flow was followed by a decrease which amounted to 21 per cent and lasted about seven minutes.

2. *Nitroglycerin.*—A dog which weighed 18.4 kg., with a blood flow of 135 c.c. per minute in the circumflex branch and 46 c.c. per minute in the right coronary artery, had a mean blood pressure of 140 mm. of mercury and a heart rate of 114 per minute. Nitroglycerin (1.3 mg. in 1 c.c. of saline solution) was given intravenously in fifteen seconds. Before the end of the injection, the blood pressure began to decrease and soon reached 105 mm. of mercury. At the same time, the blood flow increased in both the circumflex branch and the right coronary artery; the maximal flow was reached in less than one minute in both arteries. The maximal flow in the circumflex branch was 381 c.c., and, in the right coronary artery, 223 c.c. per minute. The heart rate when the blood pressure was lowest was 180 per minute. The blood pressure returned to its control level within fifteen minutes; the heart rate remained at about 180 during this time; the blood flow in both coronary arteries regained its control value about four minutes after the beginning of the injection (Fig. 1).

In all of the experiments the reactions to nitroglycerin were similar; sometimes, however, after the initial increase in flow, there was a decrease below the control value of as much as 29 per cent which continued as long as five minutes.

3. *Theophyllin-ethylenediamine (aminophyllin).*—A dog which weighed 18 kg. had an average flow of 116 c.c. per minute in the circumflex branch and 44 c.c. per minute in the right coronary artery. The blood pressure was 160 mm. of mercury, and the heart rate, 120 per minute. This animal was given 0.48 Gm. of aminophyllin intra-

venously in fifteen seconds. Before the end of the injection the flow increased in both right and left coronary arteries and reached its maximum in both arteries at the same time. The maximal flow was 394 c.c. per minute in the circumflex branch and 258 c.c. per minute in the right coronary artery; then the flow in both arteries decreased progressively, but very slowly. After twenty-eight minutes, the flow in both was still increased. Twenty seconds after the beginning of the injection, the mean systemic arterial pressure dropped to 90 mm. of mercury and then progressively increased, but after twenty-eight minutes it was still below the control level. The heart rate increased to 150 beats per minute.

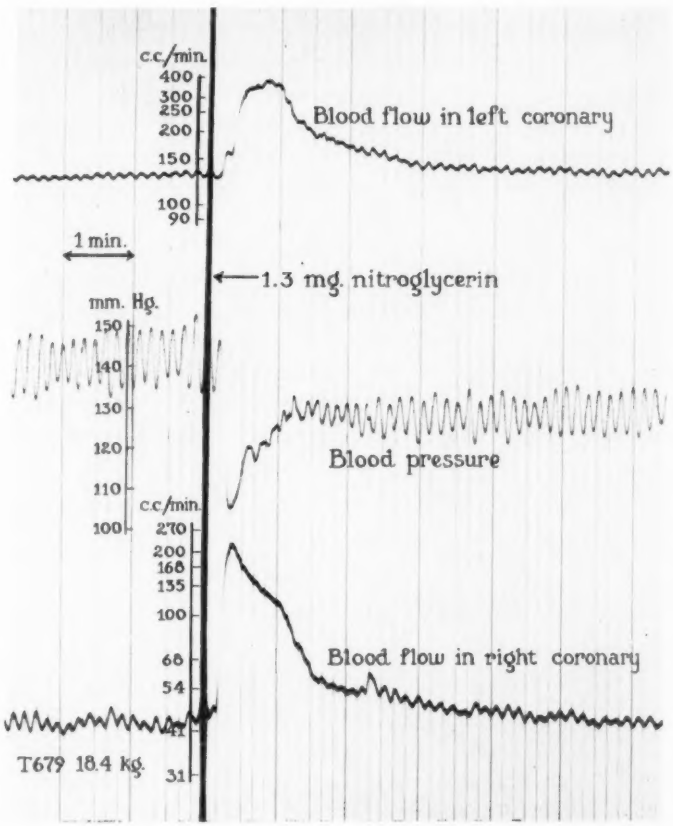


Fig. 1.—The effect of giving 1.3 mg. of nitroglycerin. This and the following figures are simultaneous photographic records of the coronary blood flow, in cubic centimeters per minute, in the circumflex branch of the left coronary artery (upper tracing), the blood pressure, in millimeters of mercury (middle tracing), and the blood flow, in cubic centimeters per minute, in the right coronary artery (lower tracing) of the dog under chloralosane anesthesia. The heavy, vertical line indicates the intravenous administration of the drug in each instance.

In some experiments the blood flow in the coronary arteries was still above the control level after the blood pressure had reached the preinjection level. Regardless of the dose of aminophyllin, there was never a significant decrease below the control level in the coronary

blood flow after the initial increase; this is in contrast to what sometimes occurred with certain of the other drugs.

In all but one experiment, the flow increased more in the right coronary artery than in the circumflex branch. The data which we have do not provide an adequate explanation for this fact.

4. *Histamine acid phosphate.*—A dog which weighed 35 kg., with a mean blood flow of 225 c.c. per minute in the circumflex branch and 68 c.c. per minute in the right coronary artery, had a mean blood pressure of 145 mm. of mercury and a heart rate of 150 beats per minute. An injection of 0.25 mg. of histamine acid phosphate, given in fifteen seconds, caused, simultaneously, a fall in blood pressure and an increased flow in both coronary arteries. The blood pressure dropped to a minimum of 110 mm. of mercury, and the heart rate increased to 180 beats per minute. As was the case with the other agents that caused hypotension, the minimal blood pressure level almost coincided with the maximal blood flow in both coronaries, which was 475 c.c. per minute in the circumflex branch and 155 c.c. per minute in the right coronary artery. The flow in the circumflex branch was back to normal one minute and thirty seconds, and, in the right coronary artery, two minutes and thirty seconds, after the injection. At the time the coronary flow had returned to its control level, the blood pressure was still relatively low, but eventually it returned to its initial level. After the increase, there was a decrease in the blood flow in the circumflex branch to a maximum of 19 per cent below the control level; the decrease lasted seven minutes. In the right coronary artery, the subsequent decrease was not significant (Fig. 2).

This is the typical reaction to such doses of histamine, when given intravenously. Occasionally, however, the blood pressure came back to its control value before the coronary blood flow. It should be stated, also, that sometimes the decrease in coronary flow which follows the initial increase may be very pronounced and of relatively long duration. In one experiment the flow decreased as much as 76 per cent in the circumflex branch and 55 per cent in the right coronary artery, and the flow in both coronary arteries remained decreased for eleven minutes.

5. *Acetyl-β-methylcholine chloride (mecholyl).*—A dog which weighed 35 kg., with a mean flow of 183.5 c.c. per minute in the circumflex branch and 65.5 c.c. per minute in the right coronary artery, and a mean blood pressure of 118 mm. of mercury, was given an injection of 0.5 mg. of mecholyl in fifteen seconds. During and immediately after the injection the flow in both arteries underwent rapid changes; there was first a rapid increase, and then a rapid decrease, but thirty seconds after the beginning of the injection the flow increased. The maximal flow in the circumflex branch was 300 c.c. per minute, and, in the right coronary artery, 101 c.c. per minute. In the right coronary artery the flow had returned to its control level after four minutes, but in the circumflex branch it was still increased thirteen minutes after the injection. The

blood pressure fell to 50 mm. of mercury within one minute after the injection and then rose progressively, but it was still decreased thirteen minutes after the injection. The heart rate increased after the injection.

6. *Papaverine.*—A dog which weighed 15 kg. had a control flow of 45 c.c. per minute in the circumflex branch and 13 c.c. per minute in the right coronary artery. The mean blood pressure was 145 mm. of mercury. At the end of an intravenous injection of 20 mg. of papaverine, given in fifteen seconds, the flow in the circumflex branch and right coronary artery increased to a maximum of 112 c.c. and 30 c.c. per minute, respectively. The blood pressure, which was decreased, did not return to its control level within that time; neither did the heart rate, which was increased. In the experiments with this drug, the increase in coronary flow was not followed by a period when the flow was below the control level (Fig. 3).

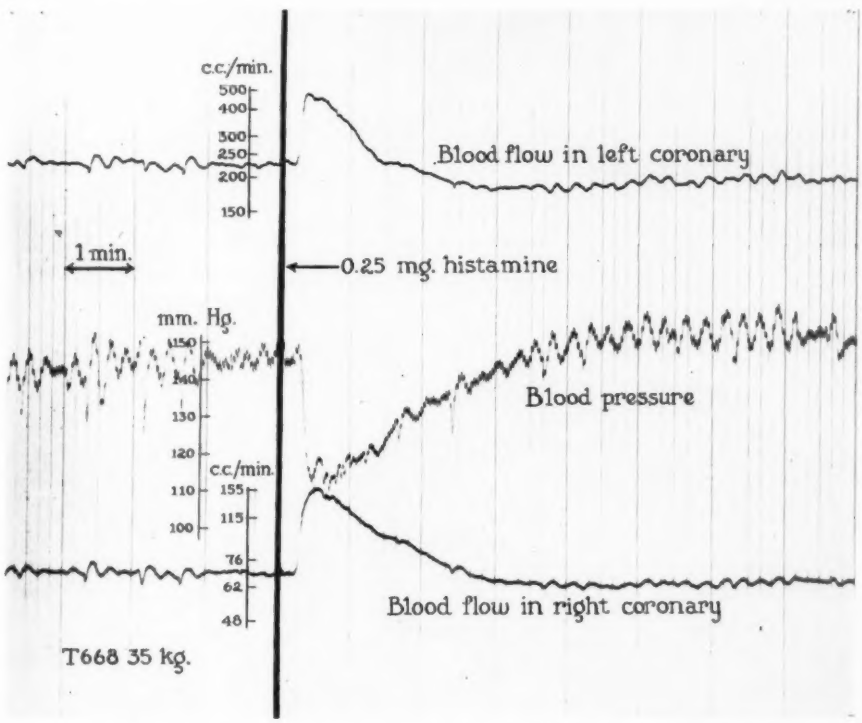


Fig. 2.—The response elicited by 0.25 mg. of histamine acid phosphate.

7. *Epinephrine.*—A dog which weighed 15 kg., with a mean flow of 30 c.c. per minute in the circumflex branch and 11 c.c. per minute in the right coronary artery, a mean blood pressure of 120 mm. of mercury, and a heart rate of 138 per minute, was given 0.025 mg. of epinephrine intravenously in fifteen seconds. Ten seconds after the beginning of

the injection, the blood pressure and the flow in both coronary arteries were simultaneously augmented. The blood pressure increased to 160 mm. of mercury; the blood flow in both coronary arteries became maximal thirty seconds after the beginning of the injection. The flow in the circumflex branch was 110 c.c. per minute, and, in the right coronary artery, 40.5 c.c. per minute. The heart rate decreased to 84 and then increased progressively when the blood pressure and coronary flow started to decrease. The blood pressure, heart rate, and the flow in both coronary arteries returned progressively to their control values in about the same time, from two to three minutes. However, the flow in the circumflex branch then decreased to a maximum of 17 per cent and remained decreased for more than ten minutes, as did the blood pressure. The flow in the right coronary artery did not undergo any significant decrease below the control values.

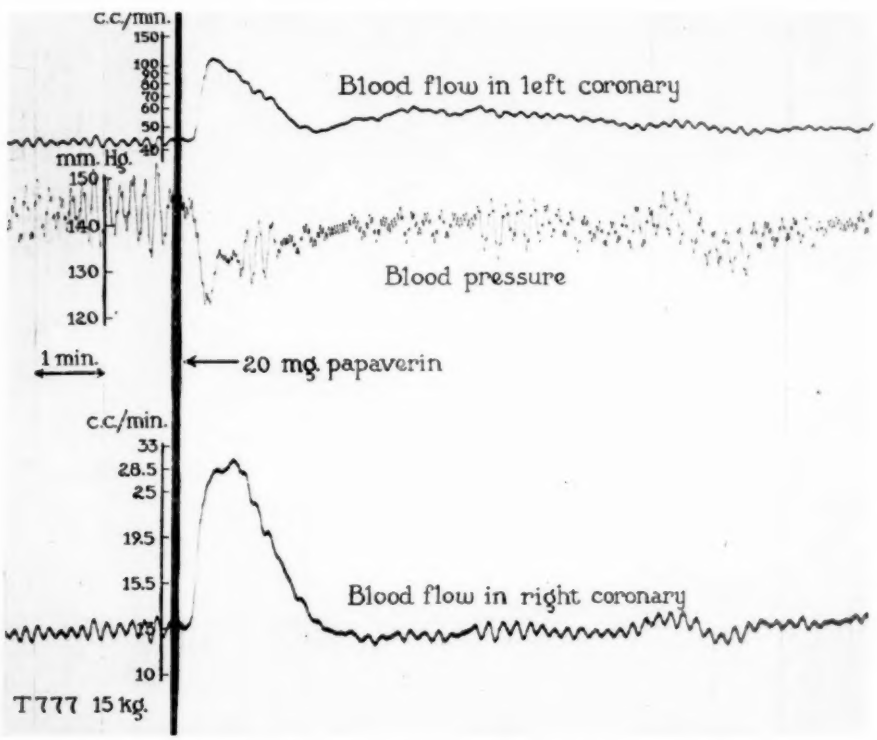


Fig. 3.—The reaction produced by 20 mg. of papaverine.

This reaction to epinephrine is typical; however, the increase in flow and blood pressure may sometimes last somewhat longer. There was not always a period of decreased flow after the initial increase. Sometimes the blood pressure had returned to, or was even below, its control value while the flow in both coronaries was still increased.

8. *Pitressin.*—A dog which weighed 15 kg. had a mean blood flow of 40 c.c. per minute in the circumflex branch and 12 c.c. per minute in

the right coronary artery. The mean blood pressure was 137 mm. of mercury, and the heart rate was 150 per minute. This animal was given 0.5 pressor unit of pitressin in fifteen seconds. The blood flow did not change very much until thirty seconds after the beginning of the injection, when the blood pressure rose to 150 mm. of mercury and the heart rate decreased to 108 beats per minute. Thirty seconds after the beginning of the injection, the blood flow decreased in both coronary arteries. The minimal flow, which was 20 c.c. per minute in the circumflex branch and less than 10 c.c. per minute in the right coronary artery, occurred three minutes after the beginning of the injection. The flow in the circumflex branch gradually returned to its control value in fourteen minutes, but in the right coronary artery the flow remained minimal longer, and, although it rose toward its control value, it was not yet back after eighteen minutes. The blood pressure had resumed its control value about one minute after the beginning of the injection, but the heart rate remained very slow; the minimal rate was 78 beats per minute, or about half the control rate (Fig. 4). Sometimes the blood pressure increased more than in the experiment described; sometimes, after the first increase, the blood pressure fell below the control level. Whatever the state of the blood pressure, the change in the coronary flow induced by pitressin was always a significant and long-lasting decrease.

9. *Pyridine-β-carbonic acid diethylamide (coramine).*—A dog which weighed 22 kg. had a mean blood flow of 130 c.c. per minute in the circumflex branch and 70 c.c. per minute in the right coronary artery. The mean blood pressure was about 128 mm. of mercury. After the injection of 500 mg. of coramine in fifteen seconds, the blood pressure decreased to 115 mm. of mercury and the blood flow in both arteries decreased for a few seconds; then the blood pressure increased to 147 mm. of mercury, and, at the same time, the blood flow increased; the flow reached a maximum of 200 c.c. per minute in the circumflex branch and 98 c.c. per minute in the right coronary artery; the blood pressure returned to normal four minutes after the beginning of the injection, but, even so, the blood flow was still increased in the circumflex branch, in which the flow had not yet resumed its control value eight minutes after the injection. In the right coronary artery the flow was back to normal after two minutes (Fig. 5). This reaction was very much the same as that in all of the other experiments, although in some of them the blood pressure did not increase significantly. The effect of coramine on the blood pressure in these experiments was in striking contrast to its effect in another group of experiments in this laboratory, in which, in dogs under pentothal sodium anesthesia, it always lowered the blood pressure.

10. *Atropine sulfate.*—A dog which weighed 20 kg. had a mean blood flow of 111 c.c. in the circumflex branch of the left coronary artery and 25 c.c. per minute in the right coronary artery. The mean blood pres-

sure was 105 mm. of mercury, and the heart rate 120 per minute. This animal was given 1.5 mg. of atropine sulfate in fifteen seconds. The blood flow in the circumflex branch and right coronary artery increased progressively to a maximum of 133 c.c. and 33 c.c. per minute, respectively. Twenty-three minutes after the injection, the flow was the same. The blood pressure did not change significantly after the injection, but the heart rate increased to 150 beats per minute. The results

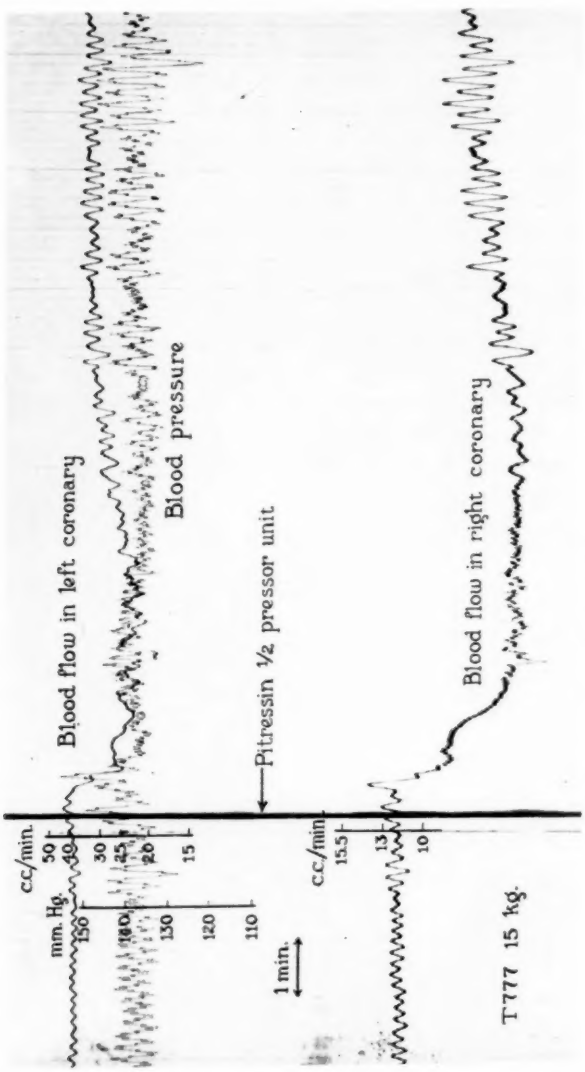


Fig. 4.—The effect of 0.5 pressor unit of pitressin.

in the other experiments with atropine sulfate were similar, except that in certain of them the blood pressure was moderately increased. In some cases the flow reached its maximum within one or two minutes and remained at this level for more than one hour.

COMMENT

The importance of the blood pressure has been emphasized so frequently in connection with the coronary circulation that the role of other factors has been somewhat overshadowed. As the data just presented clearly show, there are, in the intact animal, mechanisms which are capable of increasing the blood supply to the myocardium even when the blood pressure has been greatly lowered by the administration of certain drugs. It may be of interest to consider and attempt to evaluate the possible mechanisms by which these different drugs induce changes in coronary flow.

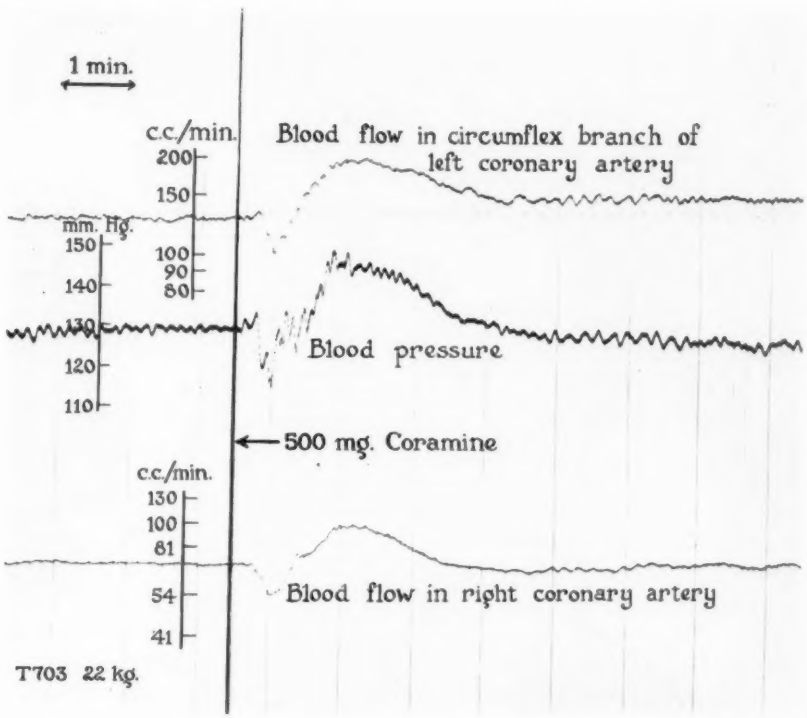


Fig. 5.—The response to 500 mg. of coramine.

Whenever the influence of drugs on the coronary circulation is discussed, the question whether they dilate the coronary vessels is always pertinent. Smith[4] and Voegtlin and Macht[5] concluded from their experiments that the nitrites produce a dilatation of the coronary vessels. Fowler, Hurevitz, and Smith[6] reported that aminophyllin aids in the development of a collateral coronary circulation in the dog, and the result, they concluded, is dependent for the most part on its dilating action on arterioles and capillaries. Anrep[7] reported that histamine dilates the coronary vessels, and he also obtained increases in the coronary flow in the heart-lung preparation and the intact animal with injections of

acetylcholine. Weinstein, Jochim, and Bohning,[8] using acetylcholine and acetyl-β-methylcholine chloride, reported an increase in the coronary perfusion flow in the isolated, fibrillating heart which had been prepared by the method of Katz, Jochim, and Bohning.[9] Under the conditions of their experiments, vasodilatation was considered the sole cause of the increased flow. Anrep[7] found that papaverine increased the coronary flow in a human heart-lung preparation. In our experiments, amyl nitrite, nitroglycerin, aminophyllin, histamine, mecholyl, and papaverine decreased the arterial blood pressure and increased both heart rate and coronary flow.

Whatever may be one's bias with respect to evidence regarding vasodilatation of the coronary vessels, it may be stated with assurance that the augmentation in coronary flow which was observed following the administration of these drugs was caused by a decrease in the effective peripheral resistance in the coronary circulation. That this is true can be demonstrated by the formula: Index of peripheral resistance varies as $\frac{\text{pressure}}{\text{flow}}$. Amyl nitrite, nitroglycerin, aminophyllin, histamine, mecholyl, and papaverine decreased the head of pressure in the coronary arteries by lowering systemic arterial pressure, which, in the absence of other influences, should decrease coronary blood flow,[10] but, since these drugs produced an augmentation of coronary flow, it must follow that the peripheral resistance of the coronary circulation was reduced. Confirmation of this conclusion was obtained from the data on the action of certain drugs by applying, under the following conditions, the formula already given. When the flow in the right and left coronary arteries is known, and when the mean blood pressure in the femoral artery is assumed to correspond to the pressure in the main branches of the coronary arteries, a close approximation of the index of peripheral resistance can be obtained. When the data from a series of observations on the effect of nitroglycerin, aminophyllin, and histamine acid phosphate were dealt with in this way, the effective peripheral resistance was found to be decidedly decreased in both coronary arteries, as shown in Table II. We are not prepared to state in exactly what way the effective peripheral resistance was reduced by all of the drugs used. The possibility that the drugs may act directly on the musculature of the coronary vessels should be considered. Since the nitrites are known to dilate the systemic blood vessels, it is very probable that they also dilate the coronary blood vessels. The dilating effect of the other drugs may be, at least in part, the result of a direct action. It is conceivable that certain drugs may act on the coronary vessels by affecting the peripheral endings of the cardiac nerves.

The possibility that certain vasomotor reflexes may influence the coronary circulation should be mentioned. Since it has been shown by Stella[11] (whose observations we have confirmed[12]) that a fall of pressure in the carotid sinus causes an increase, and a rise of pressure causes

TABLE II

CHANGES IN THE INDEX OF PERIPHERAL RESISTANCE PRODUCED BY CERTAIN DRUGS

DOG, WEIGHT	DRUG	DOSE (MG.)	INDEX OF PERIPHERAL RESISTANCE					
			RIGHT CORONARY ARTERY			LEFT CORONARY ARTERY		
			BEFORE INJECTION	AFTER INJECTION	PER CENT REDUCED	BEFORE INJECTION	AFTER INJECTION	PER CENT REDUCED
20 kg.	Epinephrine	0.25	8.02	2.59	67.7	2.04	0.61	70.1
	Nitroglycerin	1.3	6.42	1.62	74.8	1.56	0.58	62.8
1	Histamine	0.25	5.95	1.95	67.2	1.32	0.40	69.7
	Aminophyllin	240	5.31	3.11	41.4	1.29	0.82	36.4
	Epinephrine	0.10	8.33	3.22	61.3	1.67	0.54	67.7
35 kg.	Histamine	0.25	2.07	0.74	64.2	0.64	0.24	62.5
	Epinephrine	0.10	2.35	0.91	61.3	0.89	0.27	69.7
2	Nitroglycerin	1.3	2.51	1.11	55.8	0.95	0.63	33.7
	Nitroglycerin	1.3	2.07	1.06	48.8	0.86	0.62	27.9
	Aminophyllin	480	2.18	0.91	58.2	0.83	0.45	45.8

a decrease, in coronary flow, all of the drugs which we used may conceivably owe part of their influence on the coronary flow to this factor. It is also probable that the doses of the drugs used in our experiments caused an increase in cardiac output.[13, 14] This possibility must be considered, for increased cardiac output, alone, has been shown by Anrep and Segall[15] to augment the coronary flow in the innervated heart-lung preparation.

Markwalder and Starling[16] have stated that epinephrine dilates the coronary vessels. Morawitz and Zahn[17] found that the coronary blood flow was increased after the injection of epinephrine into the intact animal; Anrep,[7] confirming Rein's experiments, reported that small doses of epinephrine produced a very slight increase, and sometimes a decrease, of the coronary flow in the presence of the vagi, but the same doses in the absence of the vagi, or larger doses even in the presence of the vagi, always produced a large increase in coronary flow. In our experiments, epinephrine increased both blood pressure and coronary flow; at the same time the heart rate changed continuously.

Since the head of pressure in the coronary vessels is increased by epinephrine, it is of importance to attempt to ascertain whether the increased flow is brought about by this factor alone, or partly by this and partly by a decrease in the effective peripheral resistance. The changes in the index of peripheral resistance were ascertained by means of the formula already stated. In a series of observations, the index of peripheral resistance was shown to be greatly reduced (Table II). It is evident that the effective peripheral resistance of the coronary circulation is decreased; this, in the presence of a greatly increased blood pressure, should and does result in a much augmented coronary flow. Another factor to be considered is the possibility that epinephrine acts directly on the coronary vessels. As we have already stated, the rise in blood pressure, alone, increases coronary flow, but, through its effect on the carotid sinus mechanism, it should tend to decrease coronary

flow. The influence of changes in cardiac output may likewise have a bearing on the results with epinephrine. Whatever the various possible mechanisms are, the end result is an increased flow of blood through the coronary arteries.

With coramine, an increase in both coronary flow and blood pressure occurred. Judging from the work of Greene[18] and of Stoland and Ginsberg,[19] and from previous observations in this laboratory, we expected a fall in blood pressure. For the most part the statements made with regard to epinephrine apply as well to a consideration of the mechanism of the action of coramine, except that a significant increase in coronary flow was sometimes observed in the absence of a significant increase in the blood pressure. This would tend to show that the increase in coronary flow produced by coramine may be the result, at least in part, of a decrease in the effective peripheral resistance.

Anrep and Stacey,[20] Gruber and Kountz,[21] Melville,[22] and others have shown that pitressin decreases the coronary flow by producing a constriction of the coronary vessels. In our experiments, pitressin always produced a startling decrease in the coronary flow. The pressure increased, but sometimes it fell after a few minutes, even below the control level; usually, however, the initial increase was maintained for a few minutes before the return to the control level occurred. The heart rate was always decreased. The increase in blood pressure, alone, tends to increase the coronary flow, whereas the reflexes induced by the increase tend to decrease the coronary flow.[11, 12] Regardless of the blood pressure, however, the coronary flow was always decreased. The possibility that changes in cardiac output produced by pitressin might affect the coronary flow should not be overlooked.

Calculations of the index of peripheral resistance indicate that the reduction in coronary flow following injections of pitressin is caused by a marked increase in the peripheral resistance of the coronary circulation, which, it seems reasonable to assume, results from vasoconstriction of the coronary vessels. However, we cannot rule out the possible influence of changes in the tonus of the extravascular support except on the basis of the work of Anrep and Stacey,[20] who concluded, from a study of the effects on the heart of epinephrine, carbon dioxide, pituitary extract, and caffeine, that the influence of these substances on the strength of cardiac contraction, as measured by changes in heart volume, bore no relation to their effect on coronary blood flow.

Wiggers[23] and Anrep and Segall[15] have shown that atropine increases the coronary flow. In our experiments, atropine sulfate increased both coronary flow and heart rate. The changes in blood pressure were not great; the blood pressure increased very slightly or often not at all, so that we can say that the increase in coronary flow was caused almost exclusively by a decrease in the effective peripheral resistance of the coronary circulation.

SUMMARY AND CONCLUSIONS

Under chloralosane anesthesia, simultaneous studies were made on the effect of certain drugs on the blood flow in the right coronary artery and the circumflex branch of the left coronary artery, as well as on the mean, femoral, arterial blood pressure.

In general, the coronary flow in both the right coronary artery and the circumflex branch of the left coronary artery was greater than in trained dogs of the same size.

The blood flow in the circumflex branch of the left coronary artery was, on the average, 2.66 times that in the right coronary artery.

Changes in flow induced by the drugs which we studied were qualitatively the same in the right coronary artery and the circumflex branch.

Amyl nitrite, nitroglycerin, aminophyllin, histamine, mecholyl, and papaverine decreased the mean blood pressure and, as in the trained animal, increased both heart rate and coronary flow. The increase of coronary flow is caused by a diminution of the effective peripheral resistance in the coronary circulation.

Epinephrine increased both blood pressure and coronary flow; the increase in coronary flow was produced by an increased head of pressure and by a decrease in effective peripheral resistance.

Pitressin increased blood pressure and decreased heart rate and coronary flow; the decrease of coronary flow appears to be caused by an increase of the effective peripheral resistance in the coronary vessels.

Pyridine-β-carbonic acid diethylamide (coramine), under the conditions of our experiments, increased blood pressure and coronary flow, but the increase of coronary flow was the result, at least in part, of a decrease in the effective peripheral resistance of the coronary circulation.

Atropine sulfate increased heart rate and coronary flow, but it affected blood pressure very little; the increase in coronary flow was caused almost exclusively by a decrease in the effective peripheral resistance of the coronary circulation.

Whether the decrease in effective peripheral resistance which was produced by the various drugs was effected by active relaxation of the intrinsic musculature of the coronary vessels or by changes in the tonus of the extravascular support, or both, was not ascertained.

REFERENCES

1. Essex, H. E., Wégria, R., Herrick, J. F., and Mann, F. C.: The Effect of Certain Drugs on the Coronary Blood Flow of the Trained Dog, AM. HEART J. **19**: 554, 1940.
2. Baldes, E. J., Herrick, J. F., and Essex, H. E.: A Modification of the Thermostromuhr Method of Measuring Flow of Blood, Proc. Soc. Exper. Biol. & Med. **30**: 1109, 1933.
3. Baldes, E. J., and Herrick, J. F.: A Thermostromuhr With Direct Current Heater, Proc. Soc. Exper. Biol. & Med. **37**: 432, 1937.

4. Smith, F. M.: The Action of the Nitrites on the Coronary Circulation, Arch. Int. Med. **28:** 836, 1921.
5. Voegtlin, Carl, and Macht, D. I.: The Action of Nitrites and Drugs of the Digitalis Group on Isolated Coronary Artery, J. Pharmacol. & Exper. Therap. **5:** 77, 1913.
6. Fowler, W. M., Hurevitz, H. M., and Smith, F. M.: Effect of Theophylline Ethylenediamine on Experimentally Induced Cardiac Infarction in the Dog, Arch. Int. Med. **56:** 1242, 1935.
7. Anrep, G. V.: Lane Medical Lectures; Studies in Cardiovascular Regulation, Stanford University, 1936, Stanford University Press.
8. Weinstein, William, Jochim, Kenneth, and Bohning, Anne: The Action of Acetyl-Beta-Methylcholine and Epinephrine on the Denervated Coronary Vessels, Am. J. Physiol. **113:** 136, 1935.
9. Katz, L. N., Jochim, Kenneth, and Bohning, Anne: The Effect of the Extravascular Support of the Ventricles on the Flow in the Coronary Vessels, Am. J. Physiol. **122:** 236, 1938.
10. Wiggers, C. J.: The Physiology of the Coronary Circulation. In Levy, R. L.: Diseases of the Coronary Arteries and Cardiac Pain, New York, 1936, The Macmillan Company, p. 57.
11. Stella, G.: Some Observations on the Effect of Pressure in the Carotid Sinus Upon the Arterial Pressure and Upon the Coronary Circulation, J. Physiol. **73:** 45, 1931.
12. Wégria, R., Essex, H. E., and Herrick, J. F.: Unpublished data.
13. Grollman, Arthur: The Cardiac Output of Man in Health and Disease, Springfield, Ill., 1932, Charles C. Thomas.
14. Wégria, R.: Action de quelques médicaments (icoral, cardiazol, coramine, doryl) sur le débit cardiaque, Arch. internat. de pharmacodyn. et de thérap. **55:** 156, 1937.
15. Anrep, G. V., and Segall, H. N.: The Regulation of the Coronary Circulation, Heart **13:** 239, 1926.
16. Markwalder, Josef, and Starling, E. H.: A Note on Some Factors Which Determine the Blood Flow Through the Coronary Circulation, J. Physiol. **47:** 275, 1913.
17. Morawitz, P., and Zahn, A.: Untersuchungen über den Coronarkreislauf, Deutsches Arch. f. klin. Med. **116:** 364, 1914.
18. Greene, C. W.: Dilation of the Coronary Vessels by Certain Organic Extracts and Drugs, J. Pharmacol. & Exper. Therap. **57:** 98, 1936.
19. Stoland, O. O., and Ginsberg, A. M.: Studies on Coronary Circulation; Effect of Pyridine-Beta-Carboxylic Acid Diethylamide (Coramine) and Pentamethylenetetrazol (Metrazol) on Coronary Circulation, J. Pharmacol. & Exper. Therap. **60:** 396, 1937.
20. Anrep, G. V., and Stacey, R. S.: Comparative Effect of Various Drugs Upon the Coronary Circulation, J. Physiol. **64:** 187, 1927.
21. Gruber, C. M., and Kountz, W. B.: Some Observations on the Effect of Pitressin Upon the Cardiovascular System, J. Pharmacol. & Exper. Therap. **39:** 435, 1930.
22. Melville, K. I.: Direct Observations of Influence of Various Coronary Dilator Agents Upon Coronary Constriction Produced by Pituitary Extract, Arch. internat. de pharmacodyn. et de thérap. **44:** 316, 1933.
23. Wiggers, C. J.: The Innervation of the Coronary Vessels, Am. J. Physiol. **24:** 391, 1909.

STUDIES ON THE AURICULOVENTRICULAR CONDUCTION TIME OF NORMAL CHILDREN AND OF RHEUMATIC CHILDREN WITHOUT SIGNS OF RHEUMATIC ACTIVITY

GERTRUDE REYERSBACH, M.D., AND ANN G. KUTTNER, M.D.
IRVINGTON-ON-HUDSON, N. Y.

IN USING any laboratory test as an aid in the diagnosis of disease, it is essential to know the range of variations in normal persons. Most observers agree that, in adults, an auriculoventricular conduction time of more than 0.20 second is abnormal.[1, 2, 3] It is generally accepted that the A-V conduction time of children is shorter than that of adults. According to some authors,[3] the upper normal limit for children less than 18 years of age, with heart rates of 71 to 90 beats per minute, is 0.18 second. Another observer[4] states that the P-R interval in children less than 14 years of age should not exceed 0.16 second.

It is also generally accepted that, with comparable rates, normal persons do not show fluctuations of more than 0.02 second in the P-R interval in tracings taken at different times.[1, 5]

In studying a series of routine electrocardiograms which were taken at intervals of approximately three months on 140 rheumatic children without signs of rheumatic activity, it was noted that the conduction time was more than 0.19 second in eight children without demonstrable evidence of organic heart disease. It was also found that the P-R interval in seven cases in which there were no clinical or laboratory signs of an active rheumatic infection varied 0.04 second, or more, with comparable rates, in tracings taken at different times.

The following questions therefore arose: (1) Can a prolonged P-R interval, in the absence of other signs, be considered an indication of myocardial involvement? (2) Do fluctuations of 0.04 second, or more, in the P-R interval occur in rheumatic children in the absence of an active rheumatic infection?

Incidence of prolonged P-R intervals in rheumatic children without signs of rheumatic activity and with no evidence of organic heart disease.—The electrocardiograms of 140 convalescent rheumatic children who were classified as potential and possible cases of rheumatic heart disease, according to the criteria of the New York Heart Association,[4] were selected for study. The children ranged in age from 7 to 15 years and had been under close observation for long periods of time, varying from six months to two years. The temperature and pulse rate were taken three times daily, and hemoglobin estimations, leucocyte counts, and sedimentation rates were obtained at frequent intervals.

This work was aided by a grant from the Commonwealth Fund.
Received for publication Feb. 26, 1940.

Teleoroentgenograms and fluoroscopic examinations were made on admission and every six months thereafter. Electrocardiograms were taken every three months, or oftener. None of the children included in the study exhibited any clinical or laboratory signs of rheumatic activity during the period of observation.

The P-R interval in the majority of these children, namely, 132, was 0.18 second, or less. However, eight children (five girls and three boys), or 5.7 per cent of the group, had a conduction time of 0.20 second, or more, in the majority of the tracings. The rheumatic history, period of observation, and number of tracings taken on each of these eight children are summarized in Table I.

Since these eight children had had rheumatic fever, it was possible that the prolonged conduction time might have been the result of scarring of the conducting system. It seemed remarkable, however, that the cardiac involvement in these cases was confined entirely to the conducting system, and that no signs of organic heart disease had developed. A review of the literature showed that prolonged conduction times had occasionally been reported in apparently normal adults and children. It was thought worth while, therefore, to compare the incidence of P-R intervals of 0.19 second, or more, in our rheumatic group with that in 150 normal girls.

The length of the P-R interval in normal persons.—Although a P-R interval of 0.20 second, or more, for adults and of 0.17 to 0.18 second for children is considered abnormal by most observers, it is noteworthy that some of the control series of electrocardiograms of normal subjects published by various authors include a few exceptions. The Lewis and Gilder[1] series of fifty-two medical students included two men with conduction times of 0.20 and 0.21 second, respectively. Among 1809 midshipmen, Ferguson and O'Connell[6] found twenty-six men, or 1.5 per cent, who had conduction times of 0.21 second, or more.

A P-R interval of 0.18 second was reported by Seham[7] in an infant of 11 months, and by Burnett and Taylor[8] in an infant of 18 months. The Lincoln and Nicolson series[9] of 226 normal school children included a healthy boy of 7 years with a conduction time of 0.19 second. Alstead[10] twice found a P-R interval of 0.20 second in a group of 100 normal children whose average age was 12 years.

In addition to these instances of prolonged conduction time in normal adults and children, four cases of normal persons with markedly prolonged P-R intervals have been reported by different observers.[11]

The A-V conduction time of 150 normal girls whose ages ranged from 6 to 16 years.—Electrocardiograms were taken on 150 normal girls.* The P-R interval in the majority of these children, namely, 142, was 0.18 second, or less. Eight girls, however, or 5 per cent, had a P-R interval of 0.19 second, or more; the maximum was 0.24 second. As far as could be ascertained, none of these girls had a history of rheu-

*These children were examined through the cooperation of Dr. Luke Fleming and the Sisters of Mercy, Tarrytown, New York.

TABLE I

RHEUMATIC HISTORY AND PERIOD OF OBSERVATION OF EIGHT RHEUMATIC CHILDREN WITH PROLONGED CONDUCTION TIMES AND NO EVIDENCE OF ORGANIC HEART DISEASE OR RHEUMATIC ACTIVITY*

CASE NO.	NAME	DATE OF BIRTH	SEX	RHEUMATIC ATTACKS AND AGE AT EACH	LENGTH OF STAY AT IRVINGTON HOUSE	ELECTROCARDIOGRAMS			
						NO. OF TRACINGS	DATE	RATE	P-R (SECONDS)
1	P. McG. 3325	9/ 6/27	F	8½ P† and C, March, April, 1936 9½ Rh. fever, May, 1937	6/29/37 to 2/ 1/40	19	6/29/37 8/ 1/38 10/ 9/39	110 110 100	0.20 0.20 0.20
2	E. O'S. 3400	3/12/27	F	4 P, April to June, 1931 8 P and C, July to Aug. 1935 10 Jt. P. and epistaxis, Feb., 1937	6/14/38 to 1/28/39	10	6/14/38 10/21/38 1/27/39	90 90 90	0.22 0.22 0.21
3	C. B. 3357	12/25/23	F	11 P, Ch, and C, March, April, 1935 11½ P and Ch, fall, 1935	9/ 4/37 to 7/25/39	36	9/ 6/37 8/ 3/38 3/ 7/39	80 90 80	0.20 0.20 0.21
4	V. C. 3396	7/ 7/29	F	7 P, May, 1936 8 P, May, 1937	6/14/38 to 2/ 1/40	15	6/14/38 2/ 2/39 8/ 6/39	80 80 90	0.20 0.22 0.21
5	D. McK. 3364	5/31/29	F	7 Ch, May, 1936	9/10/37 to 11/ 1/38	14	12/17/37 10/24/38 10/31/38	80 80 80	0.20 0.20 0.20
6	H. P. 3350	5/31/39	M	6 P and C, Oct., Nov., 1935 8 C, March to May, 1937	8/24/37 to 10/11/39	29	8/25/37 5/13/38 10/ 6/39	80 80 82	0.20 0.20 0.21
7	L. S. 3500	2/16/31	M	6 P-R interval 0.20 seconds in routine physical exam. March, 1937 8 Sore throat, fever, Jt. P., ESR normal, Jan., 1939	7/11/39 to 2/ 1/40	11	7/12/39 7/17/39 9/11/39	80 88 80	0.24 0.24 0.24
8	H. V. 3055	8/23/24	M	8 P, Nov., Dec., 1932 10½ P, Jan. to March, 1935	4/25/35 to 10/17/35 1/ 6/36 to 8/ 4/36	18	9/ 7/35 2/21/36 7/20/36	80 80 80	0.38 0.38 0.20

*With the exception of Case No. 7, no tracings were taken on these children before the onset of rheumatic symptoms.

†The following abbreviations are used in Tables I and III:

P Polyarthritis
C Carditis
Rh. Rheumatic
Jt. P. Joint Pains
Ch Chorea
ESR Erythrocyte Sedimentation Rate

matic fever or chorea. They had lived in the orphanage for periods varying from one to nine years. No rheumatic manifestations had been observed during the course of their stay. On physical and fluoroscopic examination their hearts were found to be normal. Thus, no evidence of a previous rheumatic infection was obtained in any of these children. The heart rates and P-R intervals of these eight girls are presented in Table II.

TABLE II

DATA ON NORMAL GIRLS WITH P-R INTERVALS OF 0.19 SECOND, OR MORE

CASE NO.	NAME	AGE	ELECTROCARDIOGRAM		
			DATE	RATE	P-R (SECONDS)
1	E. S.	11	6/23/39	82	0.19
			9/19/39	92	0.19
2	C. U.	14	6/26/39	74	0.19
			7/10/39	106	0.19
3	A. M.	15	6/23/39	80	0.19
			9/ 4/39	90	0.19
4	M. L.	11	6/24/39	78	0.19
			9/14/39	100	0.19
5	J. L.	14	6/16/39	88	0.20
			7/10/39	88	0.21
6	E. K.	7	6/20/39	104	0.21
			7/19/39	100	0.20
			9/13/39	120	0.20
7	R. R.	13	6/26/39	78	0.20
			7/18/39	88	0.20
			9/12/39	90	0.20
8	M. M.	12	6/26/39	74	0.24
			7/10/39	82	0.20
			9/12/39	80	0.20

Fluctuations of 0.04 second, or more, in the P-R interval in rheumatic children with no evidence of active rheumatic infection.—Routine electrocardiograms which were taken, when the heart rates were comparable, over periods of six to twenty-four months on the eight rheumatic children with prolonged conduction times showed significant spontaneous variations in three instances. In two cases, the changes amounted to 0.04 or 0.05 second. In the other case, the variations were much more striking; the P-R interval varied from 0.17 to 0.40 second without significant changes in heart rate. This patient (Case 8, Table I), a boy of 11 years, was under close observation for a period of one year and showed no clinical or laboratory signs of rheumatic activity. During this time, eighteen tracings were taken at intervals of approximately three weeks. The P-R interval was greatly prolonged in ten of these tracings, ranging from 0.36 to 0.40 second; in the other eight, it was 0.17 to 0.19 second. This patient has now been followed for a period of four years. During this time he has had no signs of rheumatic activity and has not developed organic heart disease. The tendency to marked fluctuations in the P-R interval was still present when this boy was re-examined at the age of 15 years.

Spontaneous variations in the P-R interval were also noted in four children whose conduction time was 0.15 to 0.16 second in the majority of tracings. None of these children had any demonstrable clinical or laboratory evidence of rheumatic activity during the period of observation.

The spontaneous variations in the P-R interval are summarized in Table III.

Since there was no evidence that these fluctuations in the conduction time were related to an active rheumatic infection in any of these children, it seemed of interest to ascertain whether the degree of variation which we observed exceeded that which occurs in normal persons.

Lewis and Gilder[1] took repeated tracings on twenty-four medical students. In most instances, the P-R interval tended to remain constant. In one case, however, when the heart rates were comparable, a variation of 0.03 second was noted. Cohn and Swift[5] took daily tracings on six normal adults. Although these authors state that, judging from their experience, variations in the conduction time of normal persons are usually less than 0.02 second, in one of their six normal subjects there was a variation of 0.06 second.

Three observers[11a, b, c] have reported marked variations in the P-R intervals of three normal adults. The conduction time of two of these subjects varied 0.12 second (from 0.20 to 0.32 second and 0.22 to 0.34 second, respectively). The variation in the third was 0.17 second (from 0.18 to 0.35 second).

Fluctuations of 0.04 and 0.05 second in the P-R interval in normal children.—In our control series, two or three tracings were taken on the eight girls with a prolonged conduction time. Spontaneous variations of 0.04 to 0.05 second were observed in two instances.

The incidence (5.7 per cent) of prolonged conduction time in the group of 140 rheumatic children with no signs of rheumatic activity and no evidence of organic heart disease was almost the same as that in the control group of 150 normal girls (5 per cent). Since no evidence of a previous rheumatic infection could be obtained in the case of the eight normal children, it was thought that the prolongation of the P-R interval might, in certain instances, be the result of increased vagal tone.

Previous observers who have reported prolonged conduction times in normal subjects have attempted to show that the prolongation was caused by increased vagal activity, rather than by an organic lesion of the conducting system. Ferguson and O'Connell[6] succeeded in reducing the conduction time in two of their cases by the injection of atropine. Other workers[11a, b, c, d] were able to shorten the P-R interval by exercise, as well as by the injection of atropine. Levy[11d] showed that stimulation of the vagus by holding the breath or by pressure on the carotid sinus increased the degree of heart block. Following the administration of atropine, however, holding the breath and carotid sinus pressure were without effect.

TABLE III

SPONTANEOUS VARIATIONS IN THE P-R INTERVAL IN SEVEN RHEUMATIC CHILDREN WITH NO SIGNS OF RHEUMATIC ACTIVITY

CASE NO.	NAME	DATE OF BIRTH	SEX	RHEUMATIC ATTACKS AND AGE AT EACH	LENGTH OF STAY AT IRVINGTON HOUSE	ELECTROCARDIOGRAM		
						DATE	RATE	P-R (SECONDS)
1	E. O'S. 3400	3/12/27	F	See Case 2, Table I	6/14/38 to 1/28/39	6/14/38	90	0.22
						10/20/38	90	0.19
						10/21/38	90	0.22
						10/22/38	95	0.17
						1/27/39	90	0.21
2	C. B. 3357	12/25/23	F	See Case 3, Table I	9/ 4/37 to 7/25/39	9/ 6/37	80	0.20
						6/ 2/38	90	0.18
						1/ 4/39	75	0.22
						2/ 3/39	96	0.21
						3/ 7/39		
						9 A.M.	94	0.17
						noon	90	0.20
						3 P.M.	90	0.21
						5 P.M.	80	0.21
3	H. V. 3055	8/23/24	M	See Case 8, Table I	4/25/35 to 10/17/35	4/26/35	60	0.17
						9/ 7/35	80	0.38
					1/ 6/36 to 8/ 4/36	9/30/35	70	0.40
						10/ 2/35	80	0.36
						10/ 3/35	80	0.39
						10/ 7/35	70	0.17
						10/14/35	80	0.36
						1/ 7/36	70	0.17
						1/24/36	90	0.33
						2/ 7/36	100	0.18
						2/21/36	80	0.38
						3/ 2/36	70	0.40
						3/19/36	110	0.18
						4/ 7/36	80	0.38
						4/23/36	80	0.39
						5/22/36	80	0.16
						6/25/36	80	0.19
						7/20/36	80	0.20
						4/12/39	80	0.19
4	H. O. 3184	7/18/26	M	6 P, March, April, 1932 6 P, May to July, 1932	6/29/36 to 10/11/38	11/ 3/36	84	0.16
						4/13/37	82	0.21
						4/20/37	88	0.17
						5/20/37	90	0.16
						8/ 5/37	90	0.16
						2/14/38	86	0.20
						6/ 6/38	90	0.18
5	B. S. 3430	7/ 3/28	M	9 P, Aug. Sept., 1937	8/ 9/38 to 9/ 5/39	8/10/38	100	0.16
						6/ 8/39	96	0.20
						6/29/39	110	0.16
						7/19/39	110	0.18
						9/ 5/39	108	0.16
6	A. M. 3182	7/25/27	M	Unknown, Rh. family history	5/29/36 to 7/13/37	5/29/36	90	0.15
						11/ 5/36	90	0.20
						11/23/36	90	0.16
						4/27/37	70	0.16
						10/25/39	68	0.16
7	O. G. 3345	1/31/27	F	6 P, May, 1933 10 P, June, 1937	8/10/37 to 2/ 1/40	8/11/37	90	0.16
						1/22/38	108	0.18
						5/29/39	80	0.14
						10/ 2/39	84	0.17

Unfortunately, permission to study the effect of atropine on the eight normal girls with a prolonged auriculoventricular conduction time could not be obtained. Simpler methods of stimulating and inhibiting the vagus were therefore tried, both on the eight normal children and on the rheumatic children whose only abnormality was a prolonged conduction time.

Inhibition of the vagus by exercise.—The children were asked to hop, and tracings were taken when the heart rate had increased 30 to 60 beats a minute.

The P-R interval of one of the girls in the control group was decreased by 0.04 second. The conduction time in the other seven girls remained constant, or was decreased by 0.02 second, or less.

In the rheumatic group, exercise sufficient to increase the rate 30 beats per minute decreased the P-R interval from 0.20 to 0.16 second in one instance. In four other rheumatic children, although the exercise was insufficient to increase the rate significantly, changes were produced. In three, a decrease in the P-R interval of 0.04 second, or more, occurred. In the fourth child, on the contrary, there was an increase in the conduction time from 0.19 to 0.36 second (Case 8, Table I).

Holding the breath in inspiration.—Vagal activity is known to vary with the phases of respiration. In most persons, inspiration increases, and expiration decreases, the action of the vagus. Occasionally, however, the effects of inspiration and expiration are reversed.

The children were asked to take a deep breath and hold it while the tracing was being taken.

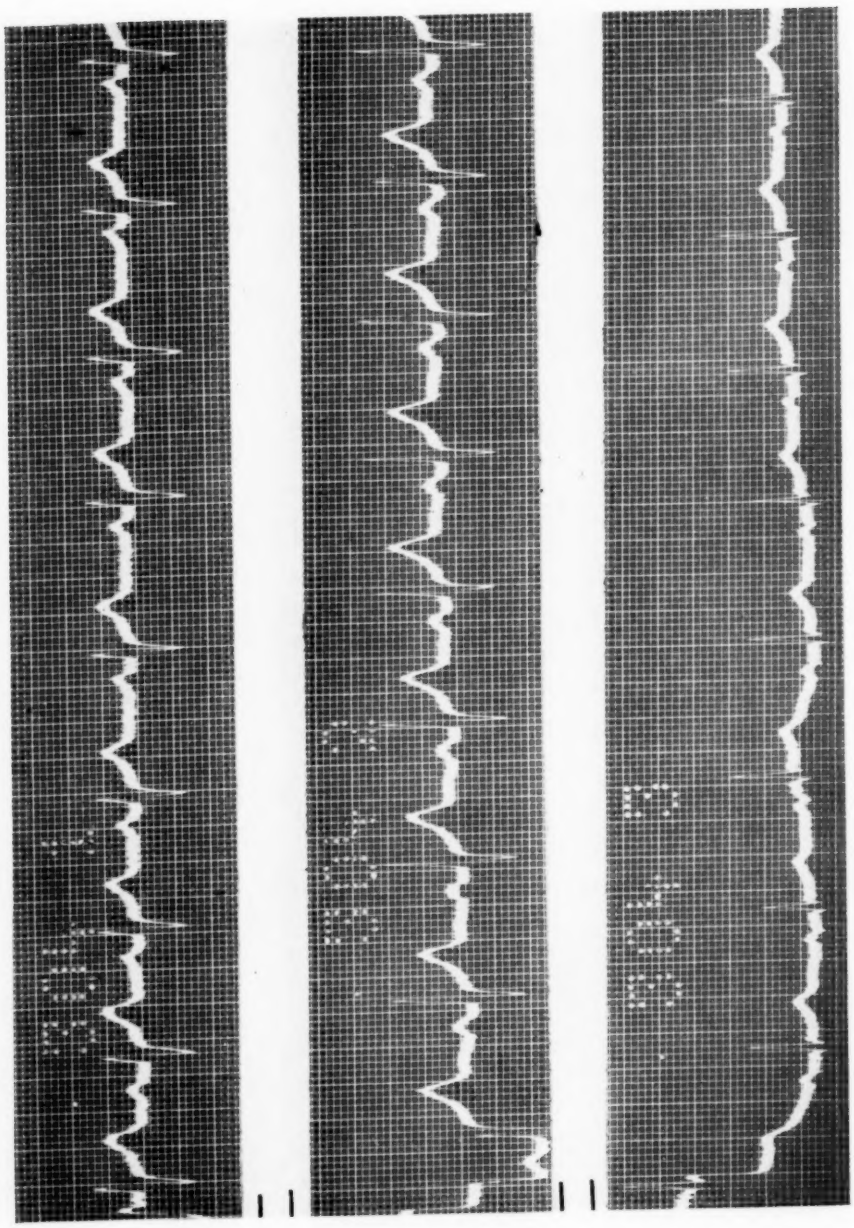
In two *normal* girls, this procedure reduced the P-R interval from 0.20 second during inspiration to 0.16 second during expiration. In another girl, although no significant change in the conduction time occurred, there was a displacement of the pacemaker from the sinoauricular to the auriculoventricular node during expiration. Nodal premature contractions were observed at the height of inspiration in one instance. The girl whose P-R interval varied spontaneously showed a marked response to holding the breath; during expiration the conduction time in certain parts of the record, instead of decreasing, increased 0.06 second. Nodal rhythm was also present occasionally during expiration.

In the *rheumatic* group with prolonged conduction time and no signs of organic heart disease, holding the breath produced no changes.

The effect of exercise and holding the breath in inspiration on six rheumatic children whose conduction times were consistently 0.17 second, or less, was studied. No significant changes were produced.

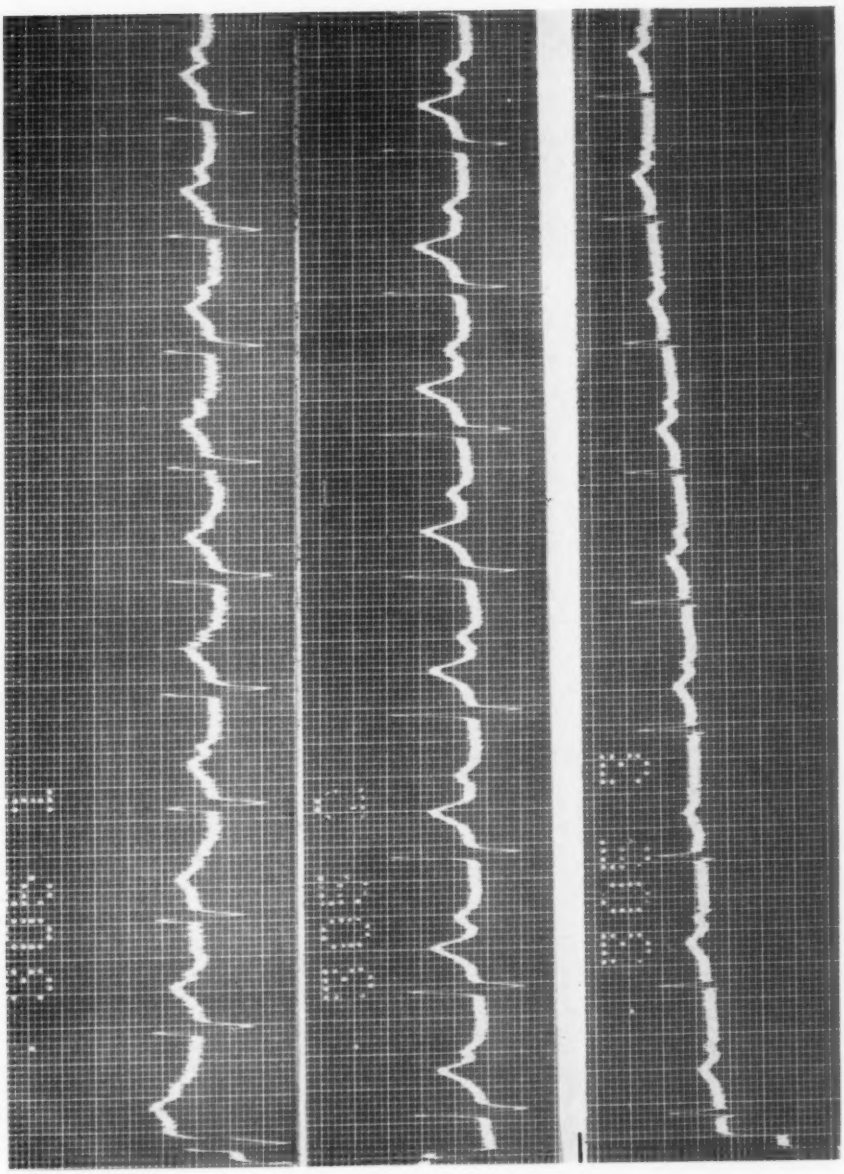
The effect of exercise and holding the breath was also studied on three children with *inactive rheumatic* heart disease who had cardiac enlargement and physical signs of organic valvular disease, associated with a prolonged conduction time. No effect was produced.

Atropine.—The effect of atropine was tried on one boy, 8 years of age, who came of a rheumatic family, but had had no clear-cut rheu-



A.

Fig. 1.—Case 8, Table 1. *A* (April 12, 1939), Routine electrocardiogram. P-R 0.19 sec. *B*, electrocardiogram taken 10 minutes later, after bending forward 20 times, P-R 0.36 sec.



B.

matic symptoms. His P-R interval was first found to be prolonged during the course of a routine physical examination at the age of 6 years and has been consistently prolonged since that time.

The intravenous injection of 1.0 mg. of atropine produced an increase in rate from 80 to 160 beats per minute, with a reduction of the conduction time from 0.24 to 0.17 second. Thirty minutes after the injection the rate dropped to 120 beats per minute, and the conduction time increased to 0.20 second. The P-R interval in the control tracing, when the rate was 80 beats per minute, was 0.24 second. The importance of the role of the vagus in this case was demonstrated in the following way: Complete heart block was easily induced by pressure on the eyeballs; following the administration of atropine, eyeball pressure had no effect.

In two children with inactive rheumatic heart disease, cardiac enlargement, and physical signs of organic valvular disease, associated with a prolonged conduction time, the intravenous injection of 1.0 mg. of atropine decreased the P-R interval 0.04 second.

In the early stages of acute rheumatic fever, in cases in which the conduction time was prolonged, Bruenn[12] and Keith[13] found that atropine shortened the P-R interval considerably. This suggests that the prolongation of the conduction time which occurs so frequently during the course of an acute rheumatic attack may be caused by an action on the vagus of toxins which are produced during the course of the infection. In our two patients with early organic heart disease and no signs of rheumatic activity, the reduction in the P-R interval was much less striking (0.04 second) than that observed in the active stage of the disease by Bruenn and Keith.

DISCUSSION

The majority of observers agree that the A-V conduction time of children is usually shorter than that of adults and tends to increase with age. Unfortunately, no study of a series of electrocardiograms taken on the same child at yearly intervals has been reported. It is, therefore, not known how much the conduction time of any given person tends to increase with age, or whether an increase of more than 0.02 second (which might be caused by the difference between the heart rates of young children and adults) actually occurs in every case.

In the opinion of most observers, P-R intervals of 0.19 second, or more, in children less than 16 years of age, are considered abnormal. It is of interest, however, that three observers[9, 10] have reported the occurrence of conduction times of 0.19 and 0.20 second in normal children.

In our series of 150 *normal* girls, whose ages ranged from 6 to 16 years, eight, or 5 per cent, had a P-R interval of 0.19 second, or more, with a maximum of 0.24 second. None had a history of rheumatic fever or chorea, and no evidence of rheumatic heart disease was found.

Prolongation of the conduction time in a child with a rheumatic history but no demonstrable heart disease, whose infection is apparently

quiescent at the time of the examination, is usually interpreted as a definite indication that cardiac involvement has occurred. P-R intervals of more than 0.18 second have been reported so rarely in normal children that the accidental discovery of prolongation of the conduction time in the course of a routine physical examination suggests that there may have been a previous, unrecognized rheumatic infection. This is not necessarily the case, however, for prolongation of the conduction time does occur in normal young adults and in normal children. It was thought of interest to consider what factors, other than a rheumatic infection, might cause prolongation of the P-R interval in children.

It is well known that a disturbance in conduction may occur during the course of diphtheria and, occasionally, during pneumonia, influenza, and typhoid fever. In all of these infections, however, the prolongation of the P-R interval usually disappears as the patient recovers.

The occurrence of P-R intervals of 0.20 second, or more, in normal individuals has been explained in various ways. Meyer[11a] thought that it might indicate a congenital abnormality of the His bundle. Reid[11b] was of the opinion that it might be caused by either a congenital malformation of the bundle of His or abnormal activity of the vagus. Ferguson and O'Connell,[6] Marzahn,[11c] and Levy[11d] considered that the prolonged conduction times which they observed were probably the result of increased vagal tone. These authors found that atropine markedly reduced the length of the P-R interval in their cases. On the other hand, it has been shown by Bruenn[12] and Keith[13] that, in normal subjects with short P-R intervals (0.17 second, or less), atropine does not reduce the conduction time significantly. These observations suggest that only when the prolongation of the P-R interval is related to unusual activity of the vagus does atropine reduce the conduction time.

Unfortunately, the use of atropine in our control group of children with prolonged conduction times was not feasible. The effect of simpler methods of stimulating and inhibiting vagal activity, such as exercise and holding the breath, was therefore studied. The results were compared with those which were obtained in a group of rheumatic children who had prolonged P-R intervals but no demonstrable organic heart disease or signs of rheumatic activity. It was found that spontaneous variations of 0.04 second, or more, occurred in both groups. Exercise reduced the conduction time significantly in two of the normal and four of the rheumatic children. In three of the rheumatic children, although the exercise was not sufficient to produce a marked increase in heart rate, it apparently stimulated the sympathetic system, for the P-R intervals were reduced from 0.06 to 0.04 second. In another rheumatic boy, exercise (bending forward 20 times while sitting in a chair) seemed to produce a feeling of apprehension, and the conduction time, instead of being decreased, was increased by 0.17 second.

Other phenomena which are thought to be the result of vagal activity, namely, shortening of the P-R interval during expiration, shifting of the pacemaker, and nodal rhythm during expiration, were observed

with approximately the same degree of frequency in the normal and the rheumatic group. The similarity of response in the two groups suggests that the prolongation of the conduction time which is occasionally found in rheumatic subjects with apparently normal hearts may be caused by increased vagal activity, rather than by a specific injury of the conduction system.

When an increase of 0.04 second, or more, in the conduction time occurs during the course of an acute rheumatic infection, it is interpreted as a definite sign of cardiac involvement; in a rheumatic child with no signs of rheumatic activity, it raises the suspicion that the rheumatic process is becoming active. On the other hand, a decrease in the conduction time in rheumatic children suggests that the myocardial lesions are healing.

In view of our observations that significant changes in the P-R interval may occasionally occur in normal, as well as in rheumatic, children, such changes, in the absence of other positive signs, should be interpreted with caution. Significant variations occurred not only in rheumatic children with prolonged conduction times who had no detectable signs of rheumatic activity, but were also occasionally observed in four rheumatic children whose P-R intervals were usually from 0.15 to 0.16 second.

It is our impression that no simple explanation of these phenomena is possible. The action of the vagus is extremely complex and varies not only with vagal tone, but also with the activity of the opposing (sympathetic) system. Furthermore, although it is thought that the cardiac impulse in each person usually follows the same path, this may not be true in every case. For instance, in cases of the so-called Kent conduction mechanism[14] there is evidence for the existence of more than one anatomic pathway. It seems possible that spontaneous fluctuations as striking as those which we observed in Case 8 (Table I) may be caused by the fact that the impulse travels by different pathways at different times.

CONCLUSIONS

1. The electrocardiograms of 150 *normal* girls, whose ages ranged from 6 to 16 years, were studied. The A-V conduction time was prolonged (to 0.19 second, or more) in eight, or 5 per cent, which is a higher incidence than has previously been reported.

2. The incidence (5.7 per cent) of prolongation of the A-V conduction time (to 0.20 second, or more) in a group of 140 *rheumatic* children with no detectable signs of rheumatic activity and no demonstrable evidence of organic heart disease was nearly the same as that among the 150 normal girls.

3. Occasionally, spontaneous variations in the P-R interval occurred, both in normal and rheumatic children with prolonged conduction times who had no detectable signs of rheumatic activity. An increase

in the P-R interval was also observed in four rheumatic children with an apparently inactive rheumatic infection whose conduction times were usually 0.15 to 0.16 second.

4. The effect of stimulating and inhibiting the vagus by exercise and holding the breath was studied on normal and rheumatic children with prolonged A-V conduction who showed no evidence of rheumatic activity. The results in the two groups were essentially the same and suggest that prolongation of the P-R interval in children with normal hearts may be the result of increased vagal activity, rather than specific injury of the conduction system. Our observations are in accord with those of Ferguson and O'Connell, namely, that prolongation of the P-R interval is not in itself a reliable index of myocardial involvement.

5. In the absence of other abnormalities, the clinical significance of an increase or decrease in the P-R interval in rheumatic children remains doubtful. Spontaneous variations in the A-V conduction time of normal persons have been reported by other workers, as well as by ourselves.

The authors are indebted to Dr. Arthur C. DeGraff for many helpful suggestions throughout the course of this investigation.

REFERENCES

1. Lewis, T., and Gilder, M. D.: The Human Electrocardiogram; a Preliminary Investigation of Young Male Adults, to Form a Basis for Pathological Study, Phil. Tr. Roy. Soc. **202**: 351, 1912.
2. Pardee, Harold E. B.: Clinical Aspects of the Electrocardiogram, New York, 1933, Paul B. Hoeber, Inc.
3. Ashman, R., and Hull, E.: Essentials of Electrocardiography, New York, 1937, The Macmillan Company.
4. Nomenclature and Criteria for Diagnosis of Diseases of the Heart, New York Heart Association, 1939.
5. Cohn, A. E., and Swift, H. F.: Electrocardiographic Evidence of Myocardial Involvement in Rheumatic Fever, J. Exper. Med. **34**: 1, 1924.
6. Ferguson, D. O., and O'Connell, J. T.: Cardiovascular Observations, Including a Series of Electrocardiograms of 1812 Men Without Heart Symptoms, U. S. Naval M. Bull. **24**: 860, 1936.
7. Seham, M.: The Electrocardiogram in Normal Children, Am. J. Dis. Child. **21**: 247, 1921.
8. Burnett, C. T., and Taylor, E. L.: Electrocardiograms on 167 Average Healthy Infants and Children, Am. Heart J. **11**: 185, 1936.
9. Lincoln, Edith M., and Nicolson, H. B.: Hearts of Normal Children; Electrocardiographic Records, Am. J. Dis. Child. **35**: 1001, 1928.
10. Alstead, S.: The Heart After Diphtheria, Lancet **1**: 413, 1933.
11. (a) Meyer, P.: Troubles Fonctionnels de la conductibilité Auriculo-Ventriculaire chez un sportif, Arch. d. mal. du coeur. **18**: 772, 1925.
    (b) Reid, W. D.: Intermittent Partial Heart Block. Report of a Case, J. Lab. & Clin. Med. **132**: 734, 1928.
    (c) Marzahn, H.: Klinischer Beitrag zur Frage funktioneller Reizleitungsstörungen, Klin. Wchnschr. **15**: 486, 1936.
    (d) Levy, R. C.: Partial Heart Block Due to Increased Vagus Action; A Case Report, Ann. Int. Med. **12**: 1525, 1939.
12. Bruenn, H. G.: The Mechanism of Impaired Auriculo-Ventricular Conduction in Acute Rheumatic Fever, Am. Heart J. **13**: 413, 1937.
13. Keith, J. D.: Overstimulation of the Vagus Nerve in Rheumatic Fever, Quart. J. Med. **7**: 29, 1938.
14. Wolferth, C. C., and Wood, F. C.: The Mechanism of Production of Short P-R Intervals and Prolonged QRS Complexes in Patients With Presumably Undamaged Heart: Hypothesis of an Accessory Pathway of Auriculo-Ventricular Conduction (Bundle of Kent), Am. Heart J. **8**: 297, 1933.

THE INFLUENCE OF DIGITALIS ON THE ELECTROLYTE AND WATER BALANCE OF HEART MUSCLE

PAUL K. BOYER,* M.D., AND CHARLES A. POINDEXTER, M.D.
NEW YORK, N. Y.

THE BENEFICIAL effect of digitalis in cardiac failure is usually[1] attributed to (1) vagal slowing of the heart rate, (2) a depression of conduction, particularly at the A-V node, and (3) a direct action on the myocardium, whereby its contractile power is augmented. The mechanism by which these actions are brought about still remains rather obscure.

Within recent years, extensive studies have been made[2, 3, 4] on the electrolyte and water balance of skeletal muscle during stimulation and recovery. The development of the chloride space concept[5, 6, 7] as a means of defining the intracellular and extracellular constituents has proved to be very valuable in these investigations. Since this concept has not been applied to heart muscle, it was considered advisable to use it to investigate the influence of digitalis on heart muscle.

In considering previous investigations bearing upon this subject, the observations made on heart muscle in cases of cardiac failure are of interest. Harrison, Cullen, et al.,[8, 9, 10, 11] found that in heart failure there are a reduction in muscle potassium and an increase in sodium and water content. They also observed a reduction in potassium in experimentally produced skeletal muscle fatigue. This latter observation has been confirmed by Fenn et al.,[4] and Tipton,[12] who applied the chloride space concept. It has also been shown[12] that both calcium and the adrenal cortex hormone act to reduce the potassium loss in stimulated skeletal muscle. Mangun and Myers[13] have confirmed the fact that there is a loss of potassium in cardiac failure, and they have observed that the degree of this loss is related to the extent of cardiac damage and hypertrophy. They also observed that the potassium loss was accompanied by a reduction in phosphorus and creatine and suggested that these three changes represented only different phases of the same problem. That there is a reduction in creatine and phosphorus in heart failure has been confirmed.[14] Zwemer and Truszkowski[15] have noted that the muscle fatigue which is so prominent a feature of adrenal cortical insufficiency is accompanied by a reduction in skeletal and also cardiac muscle potassium. Britton, Silvette, and Kline[16] have demonstrated that there is also a loss of glycogen from the muscles and liver in adrenal insufficiency, and they have suggested that potassium

From the Department of Medicine, New York Post-Graduate Medical School and Hospital, Columbia University, New York.

Received for publication Feb. 23, 1940.

*Frank Melville Fellow in Cardiology.

maintenance and glycogen maintenance within the cells are intimately related. The loss of potassium from the muscle cells in cardiac failure and skeletal muscle fatigue appears to have an important relation to the impairment of function and diminution of contractile power.

Previous studies on the effect of digitalis on the potassium content of heart muscle have not yielded entirely consistent results. In dogs, Calhoun and Harrison[17] observed a marked decrease in muscle potassium after toxic and fatal doses of digitalis and no significant change after therapeutic doses. Cattell and Goodell,[18] who used the excised frog sartorius, and Wood and Moe,[19] who studied isolated heart preparations, confirmed the observation that large doses of the drug caused loss of potassium. However, Wedd[20] reported that the therapeutic action of digitalis was not the result of a lowering of the potassium content, and that when potassium loss did occur it represented a late, toxic effect of the drug. Hagen,[21] further, found that calculated therapeutic doses of digitalis caused a uniform and significant increase in the potassium content of isolated rabbit hearts, whereas toxic doses produced a marked decrease in potassium.

METHODS

Twenty adult cats, nine controls and eleven digitalized animals, were used in this study. Cats were chosen because of the recognized similarity of their digitalis response to that of man. In preliminary experiments the rabbit was found to be extremely refractory to digitalis,[22] and the electrocardiographic effects of digitalis were rather inconsistent.

Aside from the administration of digitalis, the procedure of handling controls and digitalized animals was the same. Except in one instance, the cats were examined in pairs; one was a control, and the other a digitalized animal. They were anesthetized with sodium pentobarbital, given intraperitoneally, and electrocardiographic studies were made. The average doses of sodium pentobarbital (49 mg./kg.) in the two groups were practically the same, although some individual variability was found in the amount required to maintain satisfactory anesthesia. The total duration of the anesthesia was the same for both groups, averaging about three or four hours.

Immediately before killing the animals, blood was drawn for chemical analysis; the thorax was then opened, the heart was quickly excised, and samples of the left ventricular wall were taken. A portion which weighed approximately 1 to 1.5 Gm. was taken for analysis of the water, sodium, and potassium content, and two smaller samples were removed for determination of the chloride content. Large blood vessels, fat, papillary muscles, and the septum were avoided. For water content, the muscle was dried at 105° C. until its weight became constant. The dried muscle was then ashed in platinum crucibles in a muffle furnace, at 500° to 550° C. Sodium and potassium determinations were made, in triplicate, on aliquots of the ash, sodium by the uranyl zinc acetate method of Butler and Tuthill,[23] and potassium by the chloroplatinic acid method of Shohl and Bennett.[24] Chloride content was ascertained by the method of Van Slyke and Sendroy.[25] The same methods were used in analyzing the blood serum. In addition, the specific gravity of the serum was recorded. In twelve animals the total nitrogen content was ascertained by micro-Kjeldahl digestion; the nonprotein nitrogen content, by micro-Kjeldahl digestion and aeration of the trichloracetic acid filtrate; the total protein content, by the difference between total and nonprotein nitrogen; the total

calcium content, by the Clark and Collip modification[26] of the Kramer-Tisdall method;[27] and the ionized calcium content, by calculation according to the method of McLean and Hastings.[28] The extracellular water, or chloride space, and the intracellular water were calculated from the data by the method described for skeletal muscle by Fenn et al.[4]

The method of giving digitalis was varied slightly. Five of the eleven cats were digitalized on the day of the experiment by giving rather large doses of digifoline (Ciba) intraperitoneally. The experiment was stopped when the effect of digitalis on the electrocardiogram became definite. The other six cats were given digitalis over a period of two to five days, in a dose of approximately 0.5 cat unit per day for an average, 3-kilogram cat. We did not attempt to make an exact calculation of the dosage of digitalis in relation to body weight, for it has been found that the digitalis response of cats, like that of man, is variable, and not wholly proportional to body weight. The therapeutic dose of digitalis was taken to be the amount which would produce characteristic electrocardiographic changes, but no clinical or electrocardiographic evidence of intoxication.

TABLE I

MUSCLE	CONTROL CATS		DIGITALIZED CATS	
	MEAN	S. E.$_m$	MEAN	S. E.$_m$
H_2O Gm./kg. wet	768.9	±3.4	771.4	±2.1
Cl meq./kg. wet	*35.2*	±0.85	*31.67*	±0.46
Na meq./kg. wet	40.8	±2.27	41.8	±0.65
K meq./kg. wet	*61.5*	±2.01	*69.4*	±2.17
Extracellular H_2O Gm./kg.	*265.6*	±4.6	*243.5*	±2.9
Intracellular H_2O Gm./kg.	*503.3*	±5.9	*527.9*	±3.8
SERUM				
Specific gravity	1.026	±0.002	1.027	±0.002
H_2O Gm./kg.	914.2	±2.4	914.7	±2.1
Cl meq./Liter	120.4	±1.0	118.3	±1.0
Na meq./Liter	150.0	±2.7	149.0	±2.2
K meq./Liter	5.77	±0.45	5.26	±0.75
Ca^{++} meq./Liter	2.80	±0.05	2.76	±0.06
Protein per cent	5.7	±0.3	5.7	±0.4
Total Ca per cent	11.25	±0.4	11.02	±0.25

RESULTS

The results of the chemical analyses are given in Table I. The standard error of the mean was calculated by the usual formula. Differences between the means were related to the standard error of the difference in order to derive the probability of true significance. The means which were found to differ significantly are shown in italics.

In this series of cats, the significant chemical changes caused by digitalization were an increase in potassium and intracellular water and a decrease in chloride and extracellular water. No other significant alterations occurred.

DISCUSSION

The concentration of the calcium ion in the serum was estimated because of the synergism which is known to exist between calcium and digitalis.[29] In dealing with a problem which involves the permeability of cell membranes to other electrolytes, calcium, because of its essential role in the formation and maintenance of protoplasmic membranes,[30]

must be considered. An appreciable variation in the calcium-ion concentration might conceal or exaggerate the effects of digitalis. Perhaps, also, digitalis might exert some of its effect by varying the calcium-ion concentration. However, as far as can be ascertained from this study, digitalis has no effect on the ionized calcium of the blood. The observed variability in ionized calcium may possibly explain some of the differences in the reaction of animals to calculated doses of digitalis.

Judging from the results of this study, we believe that the effect of digitalis on heart muscle appears to be quite like that of the adrenal cortex hormone, in that it acts to maintain the potassium within the cell. This action is accompanied by an increase in the hydration of the muscle cell. Both the skeletal muscle weakness caused by adrenalectomy and the myocardial weakness associated with cardiac failure are accompanied by a decrease in intracellular potassium; and the improvement in contractile power brought about by the administration of adrenal cortex hormone and digitalis, respectively, may be definitely related to the resultant restoration of potassium to the intracellular position, where its presence is essential for the maintenance of vital processes.

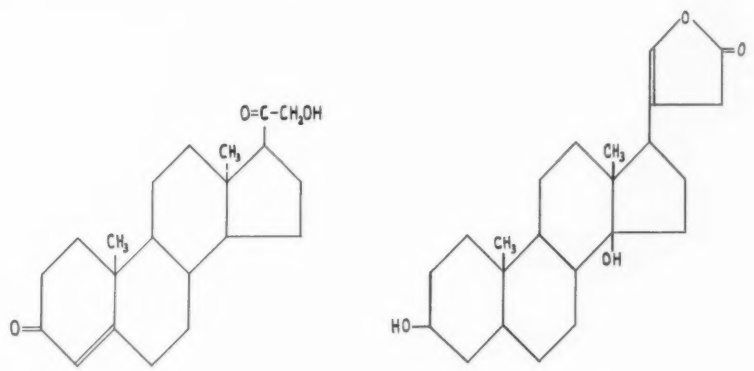


Fig. 1.—The chemical structure of desoxycorticosterone is the same as that of the crystalline adrenal cortex hormones A and B, which were isolated by Kendall, with the exception that there is an O or OH at C_{11}. Digitoxigenin is the aglycone and active portion of digitoxin, and is similar in structure to the aglycones of all the digitalis group of cardiotonic drugs.

The striking similarity in chemical structure between digitalis and the adrenal cortex hormone (Fig. 1) also suggests that they may have similar actions. It has been supposed by Zwemer and Truszkowski,[15] and others, that the action of the adrenal cortex hormone is related to differential permeability of cell membranes. The fact that calcium has a cell membrane role suggests that digitalis may act similarly. Recently, Zwemer and Lowenstein[31] have found that digitalis glucosides lower plasma potassium levels and prolong life in adrenalectomized animals;

this is a systemic action like that of the adrenal cortex hormone. The plasma potassium levels in our digitalized animals were slightly lower than in the controls, although, by the usual standards, the difference was not statistically significant. Further investigation will be needed to demonstrate the extent to which digitalis may or may not be substituted for the adrenal cortex hormone. However, it seems probable that digitalis exerts a cortin-like action directly on the heart muscle.

CONCLUSIONS

The electrolyte and water balance of heart muscle was studied in twenty cats. In this series, therapeutic doses of digitalis produced a significant increase in the intracellular potassium and intracellular water content of the heart muscle. The amount of chloride and extracellular water was reduced.

It is suggested that the beneficial effect of digitalis in cardiac failure may be brought about, in part, by a cortin-like action upon the myocardium, whereby potassium is maintained within the cell and cell hydration is improved. This may be caused by an alteration in the permeability of the muscle cell membrane to electrolytes.

Acknowledgement is made of technical assistance by Miss Gertrude Lowell.

REFERENCES

1. White, P. D.: Heart Disease, New York, 1937, Macmillan Co., p. 547.
2. Fenn, W. O., and Cobb, D. M.: Electrolyte Changes in Muscle During Activity, Am. J. Physiol. **115:** 345, 1936.
3. Fenn, W. O.: Loss of Potassium in Voluntary Contraction, Am. J. Physiol. **120:** 675, 1937.
4. Fenn, W. O., Cobb, D. M., Manery, J. F., and Bloor, W. R.: Electrolyte Changes in Cat Muscle During Stimulation, Am. J. Physiol. **121:** 595, 1938.
5. Fenn, W. O.: Electrolytes in Muscle, Physiol. Rev. **16:** 450, 1936.
6. Peters, J. P.: Body Water, Springfield, Ill., 1935, Charles C. Thomas.
7. Hastings, A. B., and Eichelberger, L.: The Exchange of Salt and Water Between Muscle and Blood. I. The Effect of an Increase in Total Body Water Produced by the Intravenous Injection of Isotonic Salt Solution, J. Biol. Chem. **117:** 73, 1937.
8. Harrison, T. R., Pilcher, C., and Ewing, G.: Studies in Congestive Heart Failure. IV. The Potassium Content of Skeletal and Cardiac Muscle, J. Clin. Investigation **8:** 325, 1930.
9. Calhoun, J. A., Cullen, G. E., and Harrison, T. R.: Studies in Congestive Heart Failure. VII. The Effect of Overwork on the Potassium Content of Skeletal Muscle, J. Clin. Investigation **9:** 405, 1930.
10. Cullen, G. E., Wilkins, W., and Harrison, T. R.: Electrolytes in Human Tissue. II. The Electrolyte Content of Hearts and Other Tissues From Cases With Various Diseases, J. Biol. Chem. **102:** 415, 1933.
11. Wilkins, W., and Cullen, G. E.: Electrolytes in Human Tissue. III. A Comparison of Normal Hearts With Hearts Showing Congestive Failure, J. Clin. Investigation **12:** 1063, 1933.
12. Tipton, S. R.: The Effect of Cortin on the Electrolyte Changes in Cat Muscle During Stimulation and Recovery, Am. J. Physiol. **124:** 322, 1938.
13. Mangun, G. H., and Meyers, V. C.: Creatine, Potassium and Phosphorus Content of Cardiac and Voluntary Muscle, Proc. Soc. Exper. Biol. & Med. **35:** 455, 1936.
14. Herrmann, G., and Dechard, G. M.: The Chemical Nature of Heart Failure, Ann. Int. Med. **12:** 1233, 1939.
15. Zwemer, R. L., and Truszkowski, R.: The Importance of Corticoadrenal Regulation of Potassium Metabolism, Endocrinology **21:** 40, 1937.

16. Britton, S. W., Silvette, H., and Kline, R.: Carbohydrate and Electrolyte Changes in Adrenal Insufficiency in the Dog, Am. J. Physiol. **122**: 446, 1938.
17. Calhoun, J. A., and Harrison, T. R.: Studies in Congestive Heart Failure. IX. The Effect of Digitalis on the Potassium Content of the Cardiac Muscle of Dogs, J. Clin. Investigation **10**: 139, 1931.
18. Cattell, McK., and Goodell, H.: On the Mechanism of the Action of Digitalis Glucosides on Muscle, Science **86**: 106, 1937.
19. Wood, E. H., and Moe, G. K.: Studies on the Effect of the Digitalis Glucosides on Potassium Loss From the Heart of the Heart-lung Preparation, Am. J. Physiol. **123**: 219, 1938.
20. Wedd, A. M.: The Influence of Digoxin on the Potassium Content of Heart Muscle, J. Pharm. & Exper. Therap. **65**: 268, 1939.
21. Hagen, P. S.: The Effects of Digilanid C in Varying Dosage Upon the Potassium and Water Content of Rabbit Heart Muscle, J. Pharm. & Exper. Therap. **67**: 50, 1939.
22. Gold, H., and Kwit, H.: Digitalis and Calcium Synergism, Science **86**: 330, 1937.
23. Butler, A. M., and Tuthill, E.: An Application of the Uranyl Zinc Acetate Method for Determination of Sodium in Biological Material, J. Biol. Chem. **93**: 171, 1931.
24. Shohl, A. T., and Bennett, H. B.: A Micro Method for the Determination of Potassium as Iodoplatinate, J. Biol. Chem. **78**: 643, 1928.
25. Van Slyke, D. D., and Sendroy, J., Jr.: The Determination of Chlorides in Blood and Tissues, J. Biol. Chem. **58**: 523, 1923.
26. Clark, E. J., and Collip, J. B.: A Study of the Tisdall Method for the Determination of Blood Serum Calcium With a Suggested Modification, J. Biol. Chem. **63**: 461, 1925.
27. Kramer, B., and Tisdall, F. F.: The Direct Quantitative Determination of Sodium, Potassium, Calcium, and Magnesium in Small Amounts of Blood, J. Biol. Chem. **48**: 223, 1921.
28. McLean, F. C., and Hastings, A. B.: The State of Calcium in the Fluids of the Body. I. The Conditions Affecting the Ionization of Calcium, J. Biol. Chem. **108**: 285, 1935.
29. Gold, H., and Edwards, D. J.: The Effects of Ouabain on the Heart in the Presence of Hypercalcemia, AM. HEART J. **3**: 45, 1927.
30. Chambers, R.: Colloid Chemistry, New York, 1928, Jerome Alexander, Chemical Catalogue Co., Vol. II, p. 467.
31. Zwemer, R. L., and Lowenstein, B. E.: Cortin-Like Effects of Steroid Glycosides on Potassium, Science **91**: 75, 1940.

THE SIGNIFICANCE OF THE POSITION OF THE SUBJECT IN THE EVALUATION OF THE ELECTROCARDIOGRAM

L. S. Ylvisaker, M.D., and H. B. Kirkland, M.D.
Newark, N. J.

ALTHOUGH it has been recognized since the early days of electrocardiography that the form of the tracing is influenced by the position of the subject, no uniform technique has been adopted. In many instances, individual practice is determined by the facilities at hand; one of the most important considerations is space limitation, which favors the sitting position. However, in other cases it is probable that the position of the subject is a matter of chance, especially if the significance of differences in configuration which occur when the position of the subject is varied is not appreciated. The fourth edition of "Nomenclature and Criteria for Diagnosis of Diseases of the Heart" takes cognizance of the potentialities of the situation and suggests that the position of the body at the time of making the record be stated in the report. There is, however, no statement as to which position is to be preferred.

We have been interested in observing the effect of position on the T waves, as it is our feeling that erroneous diagnostic conclusions result most frequently in this connection. The literature dealing with this problem is not extensive and tends to concern itself more with attempts to explain positional variations on anatomic and physiologic grounds than with the establishment of an optimum technique. Schlomka and Reindell,[1] in their investigation of the effect upon the electrocardiogram of changing from the recumbent to the standing position, found that the T wave became less positive and, in many instances, related this to diminished cardiac reserve. They feel that this phenomenon may be used as a basis for a diagnostic test, stating that the changes tend to regress in favorable cases and to persist in the presence of impaired function. They do, however, mention the advisability of adopting a universal technique of making tracings with the subject recumbent. Leimdörfer[2] discusses positional changes in cases of latent disease and considers such changes of diagnostic importance. He regards this variability as the result of physiologic alterations in coronary blood flow. Hinrichs[3] believes that electrocardiograms made with the subject in the standing position permit one to evaluate functional changes in individual parts of the heart, and that the act of standing will render the effects of myocardial disease more apparent. He states that only minor

From the Medical Department, Prudential Insurance Company.
Received for publication Feb. 28, 1940.

positional variations occur in normal subjects, but he mentions specifically the fact that the assumption of the erect posture reduces the amplitude of the T wave.

Katz and Robinow,[4] on the other hand, maintain that changes in the position of the heart within the chest account for the variations in the electrocardiogram which occur with the shift from the recumbent to the upright position. Contributing factors are said to be rotation about various axes, displacement of the heart as a unit without rotation, and alteration in the contour of the chest cavity. The summation of these factors produces essential variations in the electrical field of the body, and changes in the configuration of various complexes result. Sanders[5] reported a case of marked postural hypotension in which changes in the electrocardiogram accompanied the fall in blood pressure which occurred with assumption of the upright position. The T wave was positive when the patient was recumbent, but it became diphasic when he stood up. Åkesson[6] emphasizes the role of "orthostatic anemia" in producing T-wave changes and discusses the influence of position, vagosympathetic balance, and alterations in coronary flow; he thinks that the last factor is the most important. Janzen,[7] although he confirmed the fact that the T wave changes in the direction of left axis deviation, observed a tendency, in most cases, toward a return to the original form when the standing position was maintained for several minutes. He interprets this observation as indicating that functional factors, as well as changes in the position of the heart, influence the configuration of the T wave. He points out, also, that positional changes appear more rarely and are less prominent in cases of cardiac disease and are not as common in older people as in young persons with labile vasomotor systems. He believes that, although no rule can be established, the most extreme T-wave changes occur when there is pronounced orthostatic tachycardia. He does not believe that a functional test can be based on the positional variations under discussion. Erkelens,[8] who found these changes in a number of healthy persons, concurs in this belief and expresses the opinion that body build has a distinct influence; the most marked variations occur when the subject is of the asthenic type. Korth,[9] although he did not emphasize positional changes, observed variable T waves under different conditions and noted that exertion had an effect in some cases. He also stressed the fact that persons with an unstable vasomotor system are most likely to show variations in the T waves.

Sigler[10] described T-wave alteration with changes in position in thirty-three normal subjects; he compared the recumbent with the standing postures, but he pointed out that changes also occur with the assumption of the sitting position. He aptly observes that the changes in some cases are so marked as to make the electrocardiogram appear abnormal and lose its identity with tracings taken in other postures.

He supports the view of Katz and Robinow in regard to the influence of adjacent structures; the T-wave changes are supposedly caused by differences in the mode of spread and retreat of the current. He also takes issue with those who would use positional changes to evaluate cardiac function.

Our interest in the problem was awakened by the discovery, in a group of apparently healthy young subjects, of T-wave changes in Leads II and III which could not be regarded as within the usually accepted normal limits. When careful cardiovascular examination failed to disclose any evidence of organic cardiac disease, further electrocardiographic studies, with special reference to the influence of position, were undertaken. In every instance, the tracings which were made with the subject in the recumbent position were entirely normal as regards T-wave configuration. In some cases, the assumption of the upright position rendered the T waves negative in Leads II and III, and many subjects had diphasic or practically isoelectric T waves in Lead II, and negative T waves in Lead III. Assumption of the recumbent position invariably produced, in Lead II, positive T waves of normal configuration and amplitude. Changes in Lead III were less constant and not so marked. An incidental observation was that, in most instances, recumbency rendered the base line more even. Eight subjects showed moderate to marked somatic tremor in the upright position, but little or none in the recumbent posture.

Having conclusively established these facts with regard to the effect of position, we extended our study by making records in the sitting and recumbent positions in every case in which there was even a suspicion of changes in the S-T segment and T wave in Leads II and III. We found that positional variation occurred invariably in our normal subjects. It also became apparent that those who showed these changes were usually young and of slender build; many were highly nervous, and, although we could find no evidence of organic heart disease, they clearly showed the characteristic signs of vasomotor imbalance. In no instance was there a sufficient change in blood pressure to warrant a diagnosis of orthostatic hypotension, and none of the subjects had complaints which suggested this condition.

In thirty-seven cases there were T-wave configurations in the original records, made when the patient was in an upright position, which warranted a suspicion of myocardial involvement of some type. In no case, after repeated examinations, was evidence of organic heart disease found. Thirty-two of these subjects were 29 years of age, or less, and five were 30, or more. There were sixteen males and twenty-one females. Twenty-five weighed ten or more pounds less than would be expected for their age and height.

Table I outlines the salient clinical features in each case, together with the relevant T-wave changes which occurred with change of position. In all but four cases, the heart rate slowed when the subject lay down, and, in eleven, the rate retardation exceeded 20 beats per

minute. Definite deviation of S-T or T-P from the isoelectric line was noted in nineteen cases. Unless otherwise stated, there was a slight QRS shift toward right axis deviation when the upright position was assumed, but the QRS changes were insignificant in all cases. It should be mentioned that in some cases the degree of positional variation later diminished, probably because the vasomotor system became more stable with increasing age. Added weight may also have been a factor.

Figs. 1 and 2 were selected from our series to illustrate striking T-wave variation with change of position.

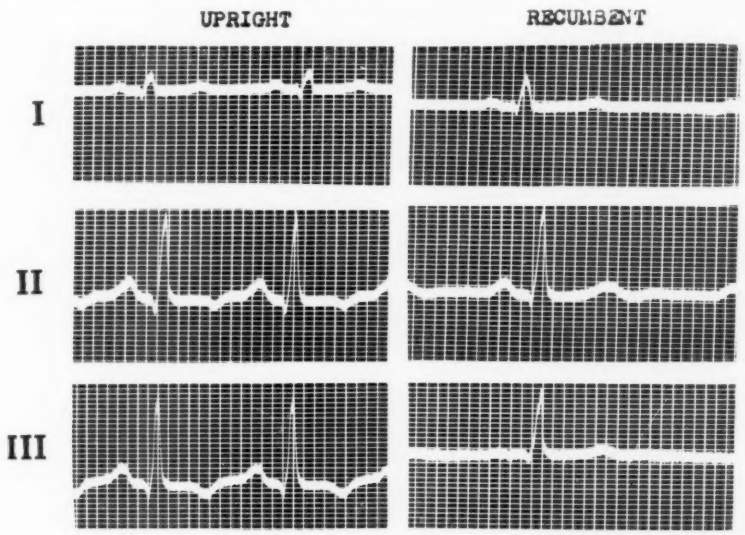


Fig. 1.—Case 5. The T waves in Leads II and III become upright in recumbency, the rate is much slower, and TP elevation is eliminated.

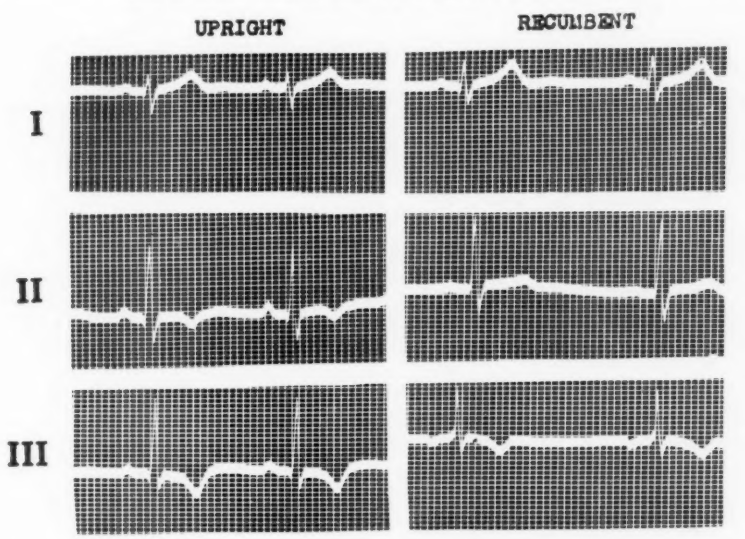


Fig. 2.—Case 33. The T waves in Lead II become upright in recumbency, with appreciable slowing of rate.

TABLE I

CASE NUMBER	RECORD NUMBER	AGE	SEX	HEIGHT	WEIGHT	DEVIATION FROM AVERAGE BUILD*	ELECTROCARDIOGRAM WITH SUBJECT UPRIGHT					ELECTROCARDIOGRAM WITH SUBJECT RECUMBENT					REMARKS
							RATE	S-T	T-P	T_2	T_3	RATE	S-T	T-P	T_2	T_3	
1	1934	26	M	5′ 11″	135	−26	96	iso.	+1, L_2	+.5	+1	80	iso.	iso.	+1.5	+1.5	
2	2368	28	F	5′ 1″	99	−22	110	−.5, L_2	+1, $L_{2,3}$	diph.	diph.	86	iso.	iso.	+3	+1	
3	2579	19	F	5′ 7″	138	+ 3	102	iso.	+.5, L_2	+1	−1.5	85	iso.	iso.	+2.5	+.5	
4	2585	22	M	5′ 11″	140	−18	70	iso.	iso.	+.5	−1	65	iso.	iso.	+1.5	diph.	
5	2602	19	M	5′ 11″	134	−23	100	iso.	+1, $L_{2,3}$	−1	−2	72	iso.	iso.	+2	+1	
6	2616	22	M	5′ 10″	135	−19	90	iso.	iso.	+1.5	−1.5	86	iso.	iso.	+2.5	−1	
7	2650	19	F	5′ 4″	118	− 6	94	iso.	+.5, L_2	diph.	−1	94	iso.	iso.	+1.5	−.5	
8	2967	28	M	6′ 4″	156	−37	82	iso.	iso.	+.5	−1	65	iso.	iso.	+1.5	−1.5	T_1: +1 U, +2.5 R
9	2985	18	M	5′ 11″	126	−27	92	iso.	iso.	−1	−3	70	iso.	iso.	+2	−1	
10	2992	23	F	5′ 3″	142	+18	86	iso.	iso.	+.5	−1	75	iso.	iso.	+1.5	−.5	
11	3005	32	M	5′ 7″	112	−37	100	iso.	+1, L_2	+1	−2	82	iso.	iso.	+3	+.5	Somatic tremor U
12	3011	25	M	6′ 0″	176	+ 9	100	iso.	iso.	−.5	−1	78	iso.	iso.	+1	−1	Somatic tremor U
13	3020	24	M	6′ 1″	145	−26	112	iso.	+1, L_2	+1	−.5	96	iso.	iso.	+2	+.5	
14	3055	26	F	5′ 8″	118	−25	90	−1, L_2	+.5, L_2	+.5	−2	72	iso.	iso.	+3	+1	
15	3169	26	M	5′ 8″	135	−15	100	iso.	iso.	iso.	−.5	84	iso.	iso.	+1.5	+.5	
16	3234	23	F	5′ 3″	110	−14	102	−.5, L_2	iso.	+1	iso.	88	iso.	iso.	+2	+.5	Somatic tremor U
17	3238	18	F	5′ 6″	134	+ 4	76	−.5, L_2	iso.	+1	−1.5	72	−.5, L_2	iso.	+2	−.5	
18	3258	22	F	5′ 3″	120	− 3	96	iso.	iso.	diph.	−1	78	iso.	iso.	+1	−.5	
19	3281	23	M	6′ 2″	163	−12	100	iso.	iso.	+.5	−1	96	iso.	iso.	+2	diph.	
20	3327	18	F	5′ 3″	93	−27	110	−.5, L_2	+.5, L_2	diph.	diph.	88	iso.	iso.	+1	iso.	T_1: diph. U, +.5 R

21	3337	68	M	5′ 10″	177	+ 4	100	iso.	iso.	iso.	iso.	96	iso.	iso.	+2	+.5	T_1: +.5 U, +2 R
22	3341	22	M	6′ 0″	166	+ 3	88	+.5, L_2	iso.	+.5	−.5	68	iso.	iso.	+1	diph.	Somatic tremor U
23	3360	31	F	5′ 5″	135	+ 0	92	iso.	iso.	iso.	−.5	85	iso.	iso.	+1.5	−.5	QRS axis toward left U
24	3375	21	F	5′ 4″	111	−15	106	iso.	+1, $L_{2, 3}$	diph.	−1	96	iso.	+1, L_2	+2	diph.	Somatic tremor U
25	3382	30	F	5′ 9″	140	−10	102	iso.	+.5, L_2	diph.	−1	75	iso.	iso.	+2	iso.	
26	3388	25	F	5′ 4″	114	−14	72	iso.	iso.	+.5	−.5	72	iso.	iso.	+1.5	diph.	
27	3422	20	F	5′ 6″	120	−12	100	iso.	+.5, L_2	+1	diph.	74	iso.	iso.	+2	+1	
28	3430	24	M	5′ 11″	146	−14	88	iso.	iso.	iso.	−1	88	iso.	iso.	+2.5	+1	
29	3438	36	M	5′ 9″	144	−17	88	iso.	iso.	iso.	−1.5	65	iso.	iso.	+2	−.5	QRS axis to left U
30	3459	26	F	5′ 3″	106	−19	92	iso.	+1, L_2	+1.5	diph.	62	iso.	iso.	+2.5	+1.5	Somatic tremor U
31	3465	25	F	5′ 0″	100	−17	76	iso.	iso.	+.5	−1.5	76	iso.	iso.	+2.5	−1	Somatic tremor U
32	3473	19	F	5′ 1″	112	− 3	96	iso.	+1, L_2	+1.5	iso.	84	iso.	iso.	+2.5	iso.	Somatic tremor U
33	3500	20	M	6′ 0″	139	−22	76	iso.	iso.	−1.5	−4	52	iso.	iso.	+1	−3	
34	3599	20	F	5′ 5″	103	−25	106	iso.	iso.	+.5	−1	86	iso.	iso.	+2	+1	
35	3833	20	F	4′ 11″	96	−16	102	−.5, L_2	iso.	diph.	−1	90	iso.	iso.	+2	diph.	
36	3884	18	F	5′ 5″	122	− 4	110	iso.	+.5, L_2	+.5	−1	84	iso.	iso.	+2	−.5	QRS axis toward left U
37	3890	19	F	5′ 2″	117	− 1	110	iso.	iso.	iso.	diph.	83	iso.	iso.	+2	diph.	

*Medico-Actuarial Mortality Investigation of 1912.

+ and − values refer to positive and negative deflections in mm., 1 cm. representing 1 millivolt.

L_2 and L_3, under S-T and T-P, refer to the respective leads in which deviations from the isoelectric line occurred.

iso. = isoelectric; diph. = diphasic; U = upright; R = recumbent.

Height in feet and inches. Weight in pounds, with clothing.

DISCUSSION

Judging from our observations, we believe that all electrocardiograms should be made with the subject in the reclining position. Not only would this eliminate the possibility of making certain diagnostic errors, but heart rates would be slower, and this would tend to diminish the S-T and T-P distortion which is often incident to tachycardia. Another fact of importance is that, in most cases, the base line is more even when the subject is recumbent. There have come to our attention no reasons, except that of expediency, why the sitting position should be used. In view of the conflicting statements in the literature and the observations on normal persons which we have presented, the use of positional changes to evaluate functional capacity does not seem justified.

CONCLUSIONS

1. In a series of thirty-seven normal subjects, marked changes in T-wave configuration were produced by altering the position of the body. The possibility that this may lead to diagnostic errors is emphasized.

2. The adoption of a standard electrocardiographic technique, to include the making of all tracings with the subject in the recumbent position, is advocated.

REFERENCES

1. Schlomka, G., and Reindell, H.: Beiträge zur klinischen Elektrokardiographie: Untersuchungen über das Verhalten der Herzstromkurve beim Uebergang vom Liegen zum Stehen, Ztschr. f. klin. Med. **130:** 313, 1936.
2. Leimdörfer, A.: Zur Diagnostik der latenten Herzmuskelerkrankungen, Wien. Arch. f. inn. Med. **27:** 215, 1935.
3. Hinrichs, A.: Welche diagnostischen Erkenntnisse vermittelt der Vergleich des Elektrokardiogramms beim liegenden und stehenden Menschen? Ztschr. f. Kreislaufforsch. **29:** 790, 1937.
4. Katz, L. N., and Robinow, M.: The Appearance of the Electrocardiogram in Relation to the Position of the Heart Within the Chest, Am. J. M. Sc. **192:** 556, 1936.
5. Sanders, A. O.: Postural Hypotension With Tachycardia, Am. Heart J. **7:** 808, 1932.
6. Åkesson, S.: Bemerkungen zu der Arbeit von Schlomka und Reindell, Ztschr. f. klin. Med. **131:** 687, 1937.
7. Janzen, R.: Die Aenderungen des Electrokardiogramms beim Uebergang aus dem Liegen in die aufrechte Körperstellung, Ztschr. f. d. ges. exper. Med. **103:** 671, 1938.
8. Erkelens, A. D.: The Influence of Body Posture on the Form of the Electrocardiogram, Nederl. tijdschr. v. geneesk. **81:** 4557, 1937.
9. Korth, C.: Grenzen der klinischen Elektrokardiographie, Arch. f. Kreislaufforsch. **3:** 1, 1938.
10. Sigler, L. H.: Electrocardiographic Changes Occurring With Alteration of Posture From Recumbent to Standing Positions, Am. Heart J. **15:** 146, 1938.

CHROMATROPHIC DEGENERATION AND RUPTURE OF THE AORTA FOLLOWING THYROIDECTOMY IN CASES OF HYPERTENSION

WM. B. KOUNTZ, M.D.,* AND LOUIS H. HEMPELMANN, M.D.†
ST. LOUIS, MO.

SPONTANEOUS rupture of the aorta is not an extremely rare condition. Although it was formerly believed to be caused by arteriosclerotic and syphilitic lesions, more recent studies indicate that it can occur in an aorta which appears normal grossly, and presents little or no evidence of arteriosclerosis.[1-6] Erdheim[7] was the first to discover microscopic changes of a specific type which he designated as cystic degeneration. Other forms of degeneration have since been reported. Roberts,[8] in a recent paper on cystic degeneration of the aorta, reported a single example of the condition and was able to collect twenty-seven authentic cases from the literature. In the three cases which are to be reported, the ruptured aorta was the seat of degeneration of the muscular coat typical of that described by Erdheim.[7] In each instance a thyroidectomy had been performed before the rupture occurred, and all of the patients were suffering from severe, chronic hypertension. The clinical manifestations in these three cases were so strikingly similar that, although the possibility of coincidence could not be excluded, the events are worthy of record.

REPORT OF CASES

CASE 1.—N. K. was a thirty-nine-year-old woman who first entered Barnes Hospital on the surgical service. The complaints at the time of admission were smothering spells, dyspnea, palpitation, nervousness, fine tremor of the hands, and fatigability. These symptoms had become troublesome early in 1934. When she first consulted her physician, Feb. 20, 1934, her blood pressure was 230/130. She was kept in bed one month, without improvement. Her basal metabolic rate was found to be plus 39 per cent. Examination of her urine revealed a trace of albumin and occasional granular casts. The physician made a diagnosis of thyrotoxicosis, hypertension, cardiac hypertrophy, and nephritis. She was instructed to rest from February until May, and to spend at least eighteen hours in bed each day. During this period her blood pressure did not change, and she was advised to enter Barnes Hospital. Examination at that time showed a moderate amount of orthopnea and some dyspnea on exertion. Her eyes were prominent, but there was no lid lag. Examination of the eye grounds revealed a hypertensive retinitis, with some distention of the veins and slight papilledema. The retinal vessels were tortuous, and hemorrhages and scarring were evident. The heart was enlarged to the left, and the heartbeat was rapid and regular. The aortic second sound was accentuated and had a ringing

From the Departments of Internal Medicine* and Pathology†, Washington University School of Medicine, St. Louis.
Received for publication March 6, 1940.

quality. No murmurs were noted. The blood pressure was 220/160. Her vital capacity was only 1,600 c.c. The basal metabolic rate shortly after admission was plus 73 per cent. The following day it was plus 46 per cent. Tests revealed that her kidneys had preserved the ability to concentrate urine. A faint trace of albumin, with occasional hyaline casts, was found. The nonprotein nitrogen content of the blood was normal. The patient was believed to have a malignant type of hypertension, with an increase in her basal metabolic rate. Although it was considered that the hypertension was not the cause of the thyrotoxicosis, the signs and symptoms, as well as the increased basal metabolic rate, suggested that the patient's condition might be improved by removal of the thyroid gland. In view of the rapid heart rate, dyspnea, edema, and early cardiac disease, and because at that time complete thyroidectomy was regarded as beneficial in cases of long-standing cardiac failure, it was suggested that the entire thyroid gland be removed; this was done on June 8, 1934. Convalescence was uneventful, and the patient was greatly pleased with the result of her operation. She was discharged after fourteen days of postoperative observation. The shortness of breath, nervousness, and orthopnea were diminished.

On Oct. 3 she re-entered the hospital for an examination. She had had no smothering spells and no fatigue, except that she felt weak upon climbing stairs. She was no longer troubled with dyspnea. Her weight had increased. The essential features noted at this examination were obesity, coarseness of the voice, and pitting edema of the extremities. Her blood pressure was 210/140. Her basal metabolic rate was minus 7 per cent. Examination of the eye grounds showed marked improvement. The papilledema had disappeared, although the margins were still indistinct. It was stated that the vessels appeared less tortuous, that the scars of old hemorrhages had not increased, and that no new hemorrhages were apparent.

During the next two months she was up and about for the greater part of each day, but did not work. On Nov. 8, five months after operation, she went with her husband, after dinner, for a ride in the car. He left her for a few minutes to get cigarettes in a drug store. When he returned he found her gasping for breath. He started for the hospital, which was only a few blocks away, but before he could reach it she was dead.

Autopsy (Washington University No. 5921, performed by Dr. P. Kunkel) revealed a short, obese, white woman of an hypersthenic habitus. The eyes appeared prominent. There was a transverse thyroidectomy scar in the lower part of the neck. The face was not hirsute, but the chest and breasts below the nipples were covered with coarse, black hair. The external genitalia were normal. The skin was smooth and soft. The distribution of fat seemed to be of the simple type, and was not suggestive of endocrine dysfunction. The subcutaneous tissue was increased in amount. The peritoneal cavity contained 100 c.c. of clear fluid. The left pleural cavity was filled with a clot of 300 c.c. of blood, and a small amount of serum. There was a small hemorrhage beneath the epicardium at the tip of the right auricle. The upper mediastinum was infiltrated with blood. The adventitia of the aorta was red and hemorrhagic. Dissection of the neck failed to reveal any thyroid tissue. The heart weighed 800 grams. The hypertrophy was chiefly of the left ventricle. The myocardium was firm. Except for slight thickening of the mitral valve along the line of attachment of the chordae tendineae, the valves and endocardium were normal. Numerous atheromatous plaques were distributed throughout both coronary arteries. Microscopic examination of the heart showed marked hypertrophy of the muscle cells. There was no interstitial fibrosis. The coronary vessels showed extreme thickening, with some atheromatous change at various points. The muscular walls of the blood vessels

beneath the thickened areas of the intima were slightly atrophic. There was a slight perivascular infiltration of lymphocytes in the epicardial fat.

The wall of the ascending aorta was thin, and there were little atheromatous change and no wrinkling of the intima. Just above the posterior cusp of the aortic valve there was a small, jagged tear, 1 cm. in length. The vessel wall surrounding the tear was separated into two layers. The laceration extended completely through the wall, which had allowed blood to escape into the upper mediastinum and pericardial sac. The arch and descending portions of the aorta showed no gross changes. Several sections of the aorta around the tear and at more distal points were taken for microscopic study. At the point of the tear the aortic wall was separated into two layers.

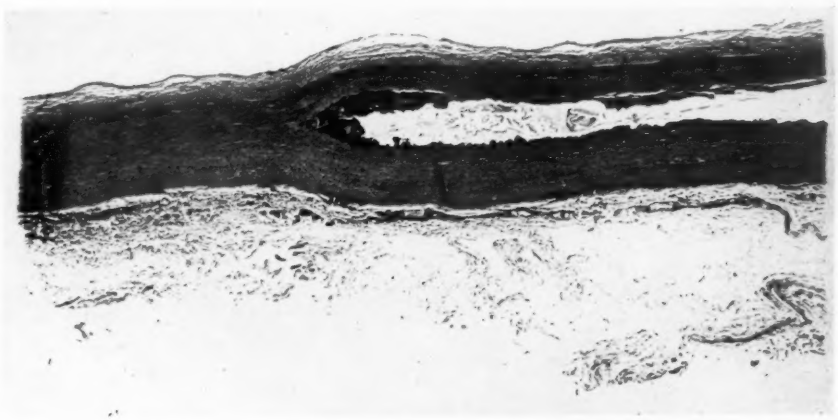


Fig. 1.—Photomicrograph (low power) of the dissecting aneurysm, showing the muscle layers split into two separate divisions. The thinner portion is toward the intimal layer.

The outer layer was composed of the adventitia and, in some places, a thin strip of media. The inner layer was formed by the intima and the greater portion of the media. A false channel extended within a short distance of the aortic ring. The most striking change in the vessel wall was the interstitial accumulation of faintly basophilic material between the elastic fibers, muscle fibers, and in the connective tissue. In several places just beneath the intima there were small areas in which muscle and elastic fibers had disappeared. Evidence of proliferation of fibroblasts was seen in only one of the areas of degeneration. The separation and degeneration of elastic muscle fibers were most marked in the inner half of the media. The interstitial material stained intensely with the metachromatic dyes. An increased amount of calcium could not be demonstrated with alizarin. The other sections, taken from various levels of the aorta, showed the same chromatrophic interstitial change, but to a less degree, and separation of the fibers was consequently less pronounced. Cyst formation was not seen in the arch and descending aorta. In some places, the elastic fibers appeared swollen and thickened, and were occasionally broken.

The Fallopian tubes were completely obliterated, and the ovaries contained simple cysts.

The remainder of the organs were essentially normal, except for the kidneys and adrenal glands. The latter weighed approximately 12 Gm. The left adrenal was thickened and nodular, and, on section, was found to contain several nodules, the largest of which measured 1 cm. in diameter. In the right adrenal there

was one small cortical nodule. Microscopic study of the adrenals showed that the nodules were composed of large, lipoid-rich, cortical cells which lacked the cord-like arrangement of the normal adrenal cortex. In many places the groups of cells were separated by dilated blood channels. The arteries in the cortex had extremely thickened walls. The right kidney weighed 150 Gm., and the left, 140 Gm. Their capsular surfaces were finely granular, and the cortex of each kidney was of approximately normal thickness. Dark-red spots were seen on the surface under the capsule, and the renal pelves were injected and thickened and likewise contained numerous small petechiae. Microscopically, the surface of the kidney was irregular because of arteriosclerotic scars. The capsule was thickened and hyalinized, particularly over the scarred areas. The walls of the small vessels were greatly thickened and hyalinized. There was some congestion of the glomeruli, but no hyalinization.

CASE 2.—H. C., a man of twenty-eight, first entered Barnes Hospital in August, 1935, with complaints of numbness of his right side and inability to focus his eyes. This had been noted three weeks before, while at work, and at that time had lasted four hours. He stated that, nevertheless, he finished his day's work, and then consulted a physician, who told him he had high blood pressure, with disease of the heart and kidneys. He told us that he had had two attacks of scarlet fever before the age of twelve. He had also had diphtheria at the age of ten, and rheumatism at the age of twenty and twenty-two. Examination revealed a man of relatively youthful appearance, with a flushed face and moderate emaciation. Examination of the eye grounds disclosed slight thickening of the arterial walls, with moderate tortuosity of the vessels; there were no exudates or hemorrhages. The tonsils were large, and pus could be easily expressed from the right one. The thyroid isthmus was enlarged. The heart rate was 120, and the heartbeat was regular. There were an apical systolic murmur and moderate cardiac enlargement. A fine, intense tremor was evident in the extended hand. The peripheral arteries were thickened. His blood pressure averaged 195/122. The basal metabolic rate on two occasions was plus 34 per cent and plus 32 per cent, respectively. The urine was normal. The concentration diuresis test showed an ability to concentrate to a specific gravity of 1.020. The phenolsulphonephthalein excretion was 45 per cent in two hours. The blood Kahn reaction was negative. Because of his infected tonsils and the urging of the consulting otolaryngologist, a tonsillectomy was performed. He returned to his physician, who gave him Lugol's solution and kept him in bed. His condition was not improved. He noted occasional shortness of breath, pounding of his heart, and, later, dizziness and transient attacks of amblyopia. His blood pressure rose to 210/135. During this interval the basal metabolic rate had been continuously high, but, on one occasion, was as low as plus 7 per cent. In May, 1936, because of his lack of improvement and the signs of increasing circulatory difficulty, he entered the hospital for a complete thyroidectomy. Following the operation his basal metabolic rate fell to minus 8 per cent. For three weeks after discharge he was given small doses of thyroid (½ gr. per day). This was discontinued because of rapidly rising blood pressure. Early in July he entered the hospital because of repeated, clonic convulsions which had occurred over a period of a week and were accompanied by headache, nausea, and vomiting. Ophthalmoscopic examination showed blurring of the disc margins, narrowing of the arteries, and exudate. His heart was enlarged to the left and downward. A rough systolic murmur, which had not been evident on the first admission, was heard at the apex. The blood pressure was 280/160. The basal metabolic rate was minus 5 per cent, but because of his serious condition it was questionable whether this represented the true value. After a few days' observation he returned home, but re-entered the hospital in October, 1936, five months after the operation, with

the complaint of violent precordial and substernal pain. His pulse was regular and not rapid; there were occasional dropped beats. A long, loud murmur, rough in quality, was heard at the base of the heart. A little later, auricular fibrillation became evident, with a large pulse deficit. His blood pressure was about 240/120. He died a few hours after admission.

Autopsy (Washington University No. 6637, performed by Dr. R. Elliott) revealed a well-developed, well-nourished white man. Except for a transverse thyroidectomy scar in the lower part of the neck, the appearance of the body was not unusual.

The left pleural cavity contained 250 c.c. of clear, straw-colored fluid. There were a few fibrous adhesions at the apex of the lung. The right pleural cavity was completely obliterated by fibrous adhesions.

The pericardial sac contained about 500 c.c. of clotted blood. The clot extended into the superior part of the mediastinum, where the upper part surrounded the proximal portions of the great vessels of the neck. When the heart was raised from its cavity, blood gushed from a large opening in the ascending aorta. The surfaces of the pericardial cavity were normal.

The heart weighed 500 Gm. The left ventricle was markedly hypertrophic. The right ventricle was of normal size and capacity. The left atrium was small, and the endocardium was thickened and opaque. There was a large, irregular hemorrhage in the interauricular septum, which was visible on the endocardial surfaces of both atria. The mitral valve and chordae tendineae were thickened. As a result of the thickening, the position of the valve was fixed, and the atrioventricular orifice was narrow. The other valves appeared essentially normal, although the aortic valve was slightly thickened. The coronary vessels arose about one centimeter above the free margin of the aortic valve. The orifice of the right coronary artery was greatly narrowed by an atheromatous plaque in the intima of the aorta. Beyond this point, the lumen of the vessel was not constricted. The left coronary vessel showed only occasional arteriosclerotic plaques. The myocardium of the left ventricle contained many fine gray foci, particularly in the papillary muscles. Microscopically, the muscle fibers of the left ventricle were greatly hypertrophied. For the most part they were widely separated. There was little interstitial fibrosis, but a considerable increase in the amount of perivascular fibrous tissue, which was not, however, arranged in a concentric manner. The mitral valve was composed of dense, fibrous tissue. Small vessels were found deep in the substance of the valve. Around one of the vessels there were concentrically placed epithelioid cells. There was no cellular infiltration elsewhere in the valve. The coronary artery showed some intimal proliferation, with atheromatous change in the thickest portion.

There was a long, linear tear in the posterior wall of the aorta, measuring 13 cm. in length. The tear began two centimeters to the right of the orifice of the left coronary artery and followed the course of the arch of the aorta, passing posterior to the great vessels. The edges of the laceration were generally smooth. There were a few, small, elevated atheromatous plaques in the intima adjacent to the lesion. The tear did not extend completely through the wall, but led into an extensive dissecting aneurysm which reached from the aortic ring to the renal arteries. The aneurysm at no point completely surrounded the aorta, but formed an irregularly shaped channel involving one-quarter of the circumference.

The channel assumed a spiral course (since it arose in the posterior part of the ascending aorta), became superior to the true lumen in the arch, was on the left in the descending portion of the aorta, and terminated in the anterior portion of the wall of the abdominal aorta. The false lumen followed the course of the celiac and renal arteries for a short distance. The walls of the aneurysm had a rough appearance. The blood within the channel was not clotted. The intima of the

aorta contained numerous, small, soft, atheromatous plaques, none of which was calcified or ulcerated. The intervening portions of the intima were smooth and yellow-tan in color. The aortic wall felt soft and inelastic.

Microscopically, the aorta showed the same lesion which was present in the first case. The essential change consisted of an increase in the amount of chromatrophic interstitial material, with resultant separation of the elastic membranes and muscle fibers. The distribution of the interstitial material was more uniform than in Case 1. In some sections, particularly in those from the ascending aorta, the muscle and connective tissue cells appeared degenerated, although large areas of tissue destruction and cyst formation were seen. Small cystic lesions, however, were frequently observed. In these regions, as well as elsewhere, the interstitial material stained intensely with metachromatic dyes, polychrome methylene blue, and toluidin blue. Sudan III and Scharlach R showed that there were small lipoid droplets in this substance.

The false channel lay in the outer half of the media in the ascending aorta, but in the descending portion it separated the vessel wall into two more or less equal parts. Fibrin and clotted blood were adherent to the walls of the channel. The tissues adjacent to the false lumen were infiltrated with inflammatory cells, chiefly polymorphonuclear leucocytes. The inflammatory change just described was confined to the media. It was patchy in distribution and most marked in the ascending aorta. The adventitia did not show fibrous thickening or perivascular infiltration. In places in which it lay close to the lumen, the tissue was infiltrated with inflammatory cells. The intima had undergone some arteriosclerotic thickening, with fatty change.

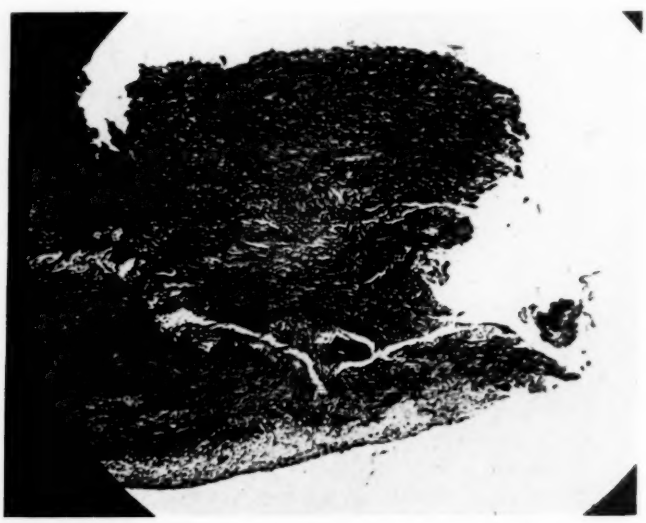


Fig. 2.—Photomicrograph (low power), showing a point of complete rupture of the aorta. The intimal surface shows no gross arteriosclerotic changes. Although, in the gross, the tear through the vessel appeared sharp, under the microscope it was quite irregular.

Nothing of importance was found in any other organs except the kidneys, which had a combined weight of 325 Gm. They were alike in size and shape. The capsules were densely adherent to granular surfaces. The cortex of each kidney was normal in thickness, but the architecture was considerably distorted by the irregular fibrosis. The pelves and ureters appeared normal. The arteries in the kidneys showed marked change. The walls of the arterioles were greatly thick-

ened, and, in many cases, hyalinized. The small arteries showed considerable intimal proliferation. The larger vessels (about the size of the arcuate arteries) showed a slight separation of the muscle fibers similar to, but not nearly as marked as, that seen in the wall of the aorta. There were a few arteriosclerotic scars in the cortex. In these regions the glomeruli were hyalinized and the tubules largely replaced by scar tissue and lymphocytes. The adrenals were normal both grossly and microscopically.

CASE 3.—W. B., a widow of twenty-seven, first came to the clinic in 1928 for removal of a small tumor on her foot. Her blood pressure at that time was normal, and, except for some periods of depression, she appeared quite well. A few years later she came in with symptoms of chronic appendicitis, and an appendectomy was performed. Her blood pressure was 120/90. In 1933, she had a smothering attack, accompanied by rattling in the throat and followed by the expectoration of frothy, bloodtinged sputum. In August, 1935, she entered the hospital because of recurrence of these smothering spells, and was found to have hypertension, which was variable in degree, with a maximum level of 236/130. Her heart was enlarged, and the electrocardiogram showed evidence of myocardial damage. There was no exophthalmos or lid lag. The retinal examination showed hazy disc margins, with no definite papilledema. The retinal arteries appeared beady because of numerous constrictions; these were thought to be the result of arterial spasm, rather than any organic change. There was marked nicking of the veins. On Oct. 22, 1935, the splanchnic nerve was excised. For a few days after the operation her blood pressure averaged 120/80, but gradually returned to its former level. It was thought previous to the operation that her case was an ideal one for splanchnicectomy, but evaluation a few weeks after the procedure indicated that no good had been accomplished. Her blood pressure gradually rose to 280/130. Her basal metabolic rate on two occasions was plus 28 per cent and plus 32 per cent, respectively, and there were rather characteristic signs of moderate thyrotoxicosis. A complete thyroidectomy was performed June 9, 1936. The basal rate fell to minus 16 per cent one month after operation. The blood pressure varied between 210 and 195, systolic, and 125 and 120, diastolic, during the postoperative period. She was observed in the clinic and given one grain of thyroid daily until July, 1937. She then stopped her thyroid medication and consulted a chiropractor, and was lost to view until November, 1937. At that time the administration of thyroid was resumed. Her blood pressure fell from 260/160 to 180/100, at which level it remained from December, 1937, to July, 1938. When she was taking two grains of desiccated thyroid daily, her basal metabolic rate averaged about minus 8 per cent. She then had a quarrel with a social worker and transferred herself to another clinic, where the hypothyroidism was not recognized or treated. Upon a visit to her home she advised one of us that she was under the care of a physician who did not want her to take thyroid, and any further attempt to persuade her to do so was inadvisable. On April 26, 1939, she entered the St. Louis County Hospital with the complaint of severe precordial pain of two hours' duration. She became unconscious and died a few minutes after admission.

Post-mortem examination (Washington University No. 8086, performed by Dr. Louis Hempelmann) revealed an enormously distended pericardial sac; it contained at least four liters of blood. There was a moderate amount of clotted blood beneath the epicardial membrane. The heart weighed 650 grams; the hypertrophy was chiefly of the left ventricle.

Microscopically, the muscle cells of the myocardium showed no change. The muscle bundles were separated by edematous fibrous tissue. There was a slight increase in the amount of perivascular fibrous tissue. The circumflex branch of

the left coronary artery showed marked intimal proliferation, with slight fatty change. The muscle fibers in the media of the vessel were separated by interstitial material which was similar to that in the aorta in the other cases, but was much less in amount. Some of the small arterioles were markedly thickened.

About 1 cm. above the free border of the aortic valve there was a transverse tear in the posterior wall of the aorta. This laceration measured 2 cm. in length. At the right border it was continuous with a shorter tear which made a right angle with the larger laceration. Upon superficial inspection the edges of the laceration seemed as smooth as if they had been cut with a knife. No arteriosclerotic plaques or other lesions were present in the arterial wall. The wall of the aorta appeared to be unusually thin. The opening in the wall led directly into the pericardial sac. There was also a small amount of clotted blood about the branches of the pulmonary arteries. Microscopic examination of various levels of the aorta was made. The essential change in each case was the interstitial accumulation of an amorphous, basophilic material between the muscle fibers and elastic fibers of the media. The amount and staining properties of this material varied with each section. The largest accumulations were found in the ascending aorta, just anterior and to the right of the laceration. Here the fenestrated elastic membranes and muscle cells were so separated by the interstitial material that at times they could scarcely be identified. In several places, in the outer half of the media, they had disappeared altogether, with the formation of small, irregularly shaped cysts. The interstitial material stained faintly with hematoxylin and was structureless except for occasional, fine fibrils. Elsewhere, even in the wall adjacent to the laceration, the interstitial material was not so plentiful, but stained more deeply with hematoxylin, as well as with the metachromatic dyes. The elastic membranes were widely separated and were broken and frayed.

The nuclei of the muscle cells were normal. The interstitial change was more marked in the inner half of the aortic wall. The interstitial material stained with basophilic dyes, as well as metachromatic stains, polychrome methylene blue, toluidin blue, methylene blue, etc.

The intensity of the metachromatic reaction in this case seemed to vary with the size of the accumulation. The larger patches appeared more serous and hence less mucoid. The Sudan III and Scharlach R stains could be demonstrated in the interstitial chromatrophic material. Alizarin failed to reveal deposits of calcium. There was no evidence of an inflammatory reaction or of efforts at repair in any section. The intima in most of the sections showed no change, although there were fat droplets in the cells underlying the endothelium. The intima immediately adjacent to the laceration was entirely normal. In the sections from the descending portion of the arch there were a few atheromatous plaques which presented the usual appearance. The adventitia was not thickened, but contained numerous erythrocytes. The vasa vasorum were not unusual.

No trace of thyroid tissue was discovered in sections from the tissues of the neck. The pleural cavities were obliterated by fibrous adhesions. The left kidney was 1.5 times the size of the right, which was about normal in size. The capsules were slightly adherent. The surface showed numerous, deep scars as large as 1 cm. in diameter and several millimeters in depth. On section, the cortex was slightly diminished in thickness. The markings were indistinct, and there were numerous, tiny, red dots arranged in a radiate manner. The cortex in the region of the scars had been reduced to a narrow rim.

Microscopically, there was moderate thickening of the arterioles in the kidneys and other organs. Numerous glomeruli were fibrotic and hyalinized, but there was little interstitial fibrosis of the kidney. The glomeruli that remained were

extremely congested. The tubular cells showed marked granular degeneration. The larger vessels had undergone intimal thickening. In a few arteries the muscle cells of the media showed chromatrophic degeneration similar to that in the coronary arteries, pulmonary arteries, and aorta.

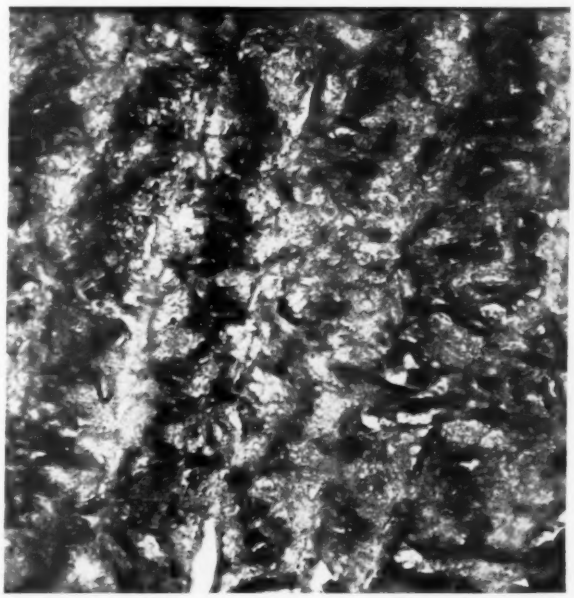


Fig. 3.—Photomicrograph (high power), showing the chromatrophic degeneration in the aortic wall. The white lines represent the degenerated material; the dark bands are muscle cells. The elastic tissue may be seen as small, sharp bands, with frayed ends. These broken ends indicate rupture of the fibers.

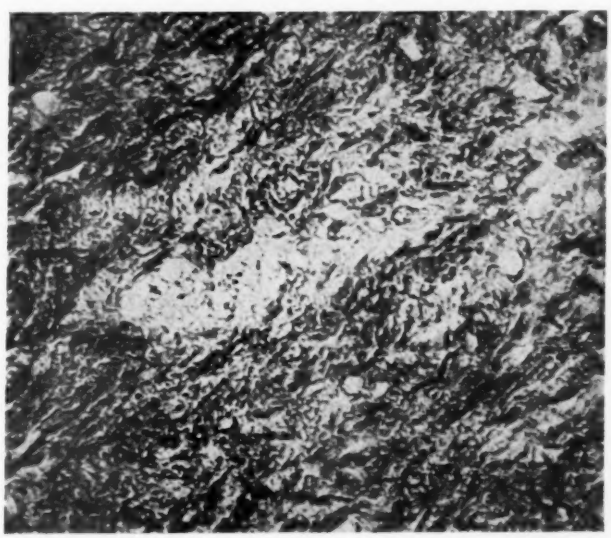


Fig. 4.—Photomicrograph (high power, special stain), showing the white degenerated material between the dark muscle bundles. The extremely large amounts of the degenerated material can be seen in this picture, as well as in many other areas of the aorta.

Sections of the hilar portions of the lungs showed extensive hemorrhage around the larger arteries. These vessels showed the same medial change as the coronary arteries and aorta. Throughout the lung, the alveolar walls were greatly thickened by an infiltration of histiocytes and fibroblasts. There were a few, small areas of organizing pneumonia.

The smaller vessels in the pancreas and in the capsule of the adrenal were moderately thickened.

DISCUSSION

It is thus seen that, in three cases of advanced and possibly malignant hypertension, complete removal of the thyroid gland was followed, in two instances at intervals of five months, and in a third instance at an interval of thirty-one months, by spontaneous rupture of the aorta. It may be significant that the third case, in which the rupture was delayed, was the only one of the three in which the patient received desiccated thyroid for a long time. It is, of course, possible that the thyroidectomy and chromatrophic degeneration in these three cases may have been a coincidence. This, however, seems improbable. It would seem more likely that the hypothyroidism and hypertension combined to produce the chromatrophic degeneration. Since spontaneous rupture of the aorta is a relatively rare occurrence, it seems improbable that this sequence of events could have been mere coincidence.

It is evident that in none of the cases were there clinical or pathologic manifestations of syphilis. No considerable atheromatous change in the aorta was apparent in the first case. In the second, there were a few, small, yellow streaks of fatty material in the ascending aorta, but none in the immediate vicinity of the laceration. The aorta of the third patient showed a few atheromatous plaques in the intima, and near the orifice of the right coronary artery there were small, elevated, atheromatous plaques in the intima adjacent to the lesions. As has been noted, none of these plaques was the seat of calcification or ulceration. It seemed improbable that they were etiologically significant in the production of the laceration. In all of the cases there was evidence of idiopathic cystic necrosis, variable in degree, of the aortic media.

The true cause of the chromatrophic degeneration of the media of the aorta is not known.[7, 9, 10] Its occurrence in three patients with hypertension who had had thyroidectomies suggests that there might be a relationship between the glandular activity and the disease of the blood vessels. Just how or what the mechanism is one cannot say. One possibly related fact is that the hearts of rabbits which have had their thyroid glands completely removed tend to accumulate mucoid substance between the muscle fibers.[11] This did not occur in human hearts. It is possible, however, that in hypertension, with strain on the aortic wall, the metabolism of the muscle of the aorta may be

greatly increased, and, therefore, that the induction of hypothyroidism, which causes an abnormality of metabolism, may bring about the deposition of abnormal products, as in myxedema.

It is true that autopsies in cases of myxedema have been notoriously few, and that, for many years, there have been almost none on patients who had not had thyroid treatment. Although our review of the literature is not complete, we have encountered no record of a case of myxedema in which aortic rupture occurred. That such accidents are infrequent must be evident. Whether the necrotic lesions of Erdheim[7] are consequent to hypothyroidism cannot be stated. Certainly the aortas of such patients have seldom been studied with the care necessary to demonstrate these somewhat subtle changes. It may be significant that relatively few patients with myxedema have excessively high arterial pressure. In the early stages of the disease the tendency to hypotension is well recognized. In long-standing hypothyroidism the elevation of blood pressure is not often great, and yields readily in most instances to treatment with desiccated thyroid.

It is our impression that complete removal of the thyroid in these cases contributed to, if it did not actually cause, a mucoid or necrotic lesion in the medial coat of the ascending aorta which so weakened the wall of that vessel that it was unable to withstand the excessively high blood pressure.

The presence of chromatrophic degeneration in the aortas of elderly persons suggests a relationship to arteriosclerosis[9] (Hempelmann). This relationship could not be definitely established in our younger group of subjects. There was some increase in the amount of calcium, but nothing more. The fact that our patients were young tended to rule out a nonspecific arterial degeneration as a cause of the disease. If one assumes a relationship between hypothyroidism and this disease, the fact that there was degenerative material in the walls of the smaller arteries emphasizes the possible importance of considering glandular dysfunction as an etiologic factor in many forms of arterial weakness and disease.

SUMMARY

In three cases of severe hypertension, in which total thyroidectomy had been done, death occurred as a result of rupture of the aorta. Although no notable change in the blood pressure occurred, the patients felt better, as a rule, immediately following the operation. In each case, varying degrees of chronic, idiopathic, aortic and arterial degeneration were found. It is suggested that this degeneration may result from a metabolic deficiency of aortic muscle under strain. It is suggested that there should be closer observation in such cases, in order to ascertain whether or not there is a relationship between disease of the glands of internal secretion and aortic and arterial disease. It is, of course,

recognized that the induced hypothyroidism and aortic cystic degeneration might have been merely coincidental.

We wish to express our appreciation to Dr. Robert Moore, Professor of Pathology, Washington University School of Medicine, and to members of the surgical service for their cooperation, as well as to Mrs. Lida W. Smith, whose financial assistance enabled us to pursue these studies.

REFERENCES

1. Resnick, W. H., and Keefer, C. S.: Dissecting Aneurysm With Signs of Aortic Insufficiency; Report of Case in Which Aortic Valves Were Normal, J. A. M. A. **85**: 422, 1925.
2. Letulle, M.: Anevrisme dissequant etendu à la totalité de l'aorte et spontanenment gueri; signes d'insuffisance aortique avec integrite parfaite des valvules sigmoides, Bull. et mém. Soc. Méd. d. hôp. de Paris **22**: 1045, 1905.
3. Borger, H.: Ueber einen Fall von geheiltem Aneurysma dissecans der Aorta, Ztschr. f. klin. Med. **58**: 282, 1906.
4. Moreau, E.: Contribution à l'étude des aneurysmes dissequants de la crosse de l'aorte, Paris, 1907.
5. Peacock, T. B.: Report on Cases of Dissecting Aneurism, Tr. Path. Soc. London **14**: 87, 1863.
6. Babes, V., and Mironescu, T.: Ueber dissezierende Arteriitis und Aneurysma dissecans, Beitr. z. path. Anat. u. z. allg. Path. **48**: 221, 1910.
7. Erdheim, J.: Medionecrosis Aortae Idiopathica Cystica, Virchows Arch. f. path. Anat. **276**: 187, 1930.
8. Roberts, J. T.: Medionecrosis Aortae Idiopathica Cystica; Report of a Case, With "Healed" Dissecting Aneurysm, Am. Heart J. **18**: 188, 1939.
9. Moritz, A. R.: Medionecrosis Aortae Idiopathica Cystica, Am. J. Path. **8**: 717, 1932.
10. Cellina, M.: Medionecrosis Disseminata Aortae, Virchows Arch. f. path. Anat. **280**: 65, 1931.
11. Webster, B., and Cooke, C.: Morphologic Changes in the Heart in Experimental Myxedema, Ann. Int. Med. **58**: 268, 1936.

OBSERVATIONS ON THE CARDIOVASCULAR SYSTEM IN MYASTHENIA GRAVIS

ALBERTO C. TAQUINI,* M.D., W. TREVOR COOKE,† M.D., AND ROBERT S. SCHWAB,‡ M.D.
BOSTON, MASS.

THE first description of myasthenia gravis was given by Thomas Willis in his "De Anima Brutorum,"[1] published in 1672. Accurate clinical descriptions of the syndrome appeared towards the close of the last century (Erb,[2] Goldflam,[3] and Jolly[4]). Studies on the subject in recent years have been made by Boothby,[5] and Kennedy and Moersch.[6]

The disease is characterized by rapid fatigue of voluntary muscles and may affect only localized groups of small muscles, e.g., the extra-ocular group and those used for chewing and swallowing, or it may seem to affect all groups of muscles in the body to an equal degree. Spontaneous remissions usually occur in about 25 per cent of the cases. The affection is not rare; Boothby has data on some 100 cases, and Viets and Schwab[7] recently reported therapeutic results in fifty cases in their special clinic.

In spite of numerous clinical reports and investigations, there is as yet no exact knowledge as to the nature of the disturbance in muscular contraction. From the work of Dale, Cannon, and others it is known that acetylcholine is liberated at the myoneural junction when muscular action takes place. This substance in some way "chemically mediates" muscular contraction. Excess acetylcholine is removed at once by an esterase (cholinesterase). In normal persons an equilibrium is maintained; in patients with myasthenia gravis this balance is disturbed.

No complete clinical studies or descriptions of cardiovascular abnormalities in myasthenia gravis are to be found in the literature, and there has been no note in any case report of any cardiac dysfunction which could be attributed to the disease. Lange[8] took roentgenkymograms in one case and felt that they were abnormal, i.e., that there were some aberrations in the contractions. Post-mortem studies on the hearts of patients with myasthenia gravis have usually shown nothing abnormal, although lymphocytic infiltration and muscle fragmentation have been reported by some.[9]

From the Cardiac Laboratory, and Paper No. 7 from the Myasthenia Gravis Clinic, Massachusetts General Hospital, Boston.

*Research Fellow in Medicine, Harvard University, from the University of Buenos Aires.

†Research Fellow in Medicine, Harvard University. Walter Myer Travelling Studentship, Birmingham University, England.

‡Assistant in Neurology, Harvard Medical School and Massachusetts General Hospital, Boston.

Received for publication March 4, 1940.

For these reasons, and because the cardiocirculatory system is a delicate neuromuscular mechanism, it was thought worth while to search for abnormalities of the cardiovascular system in a group of myasthenic patients.

Careful interrogatory and physical examinations were carried out in fourteen cases of proved myasthenia gravis. Orthodiagrams were taken in every case. Venous pressure was measured according to the method of Burwell, et al.[10] Circulation rates were estimated with ether and lobeline, or saccharin. Electrocardiograms were taken with the patients recumbent and at rest, during carotid sinus pressure, and during the injection and period of action of mecholyl (10 to 15 mg.) and of atropine (gr. 1/50). The patients who were under treatment with prostigmine bromide by mouth omitted their medication overnight, and reported at the laboratory at 8:30 in the morning, without breakfast. In advanced cases the treatment was omitted for a shorter time, but in all of the cases the examination and test were performed only when all of the symptoms of myasthenia had appeared.*

CASE REPORTS

CASE 1.—E. T., a woman, aged 19, first came to the myasthenia gravis clinic in March, 1934, with ptosis of the lids of both eyes of two months' duration and some general weakness and fatigue. Since 1937 she had been taking prostigmine (45 to 60 mg. daily) and guanidine, with excellent results.

She had no cardiac symptoms. Orthodiagraphically, her heart was normal in size. Physical examination of the heart showed nothing except a functional, pulmonary, systolic murmur. The arterial pressure was 120/80, the venous pressure, 8 cm. of water. The saccharin time was 10 sec.; the ether time, 5 sec. The electrocardiogram showed normal rhythm, a rate of 85, a P-R of 0.16 sec., a slightly prominent P_2, and late inversion T_3 (normal record).

CASE 2.—C. Z., a woman, aged 26, was referred to this hospital in October, 1938, with a story of difficulty in talking and swallowing and weakness of the facial muscles, of six months' duration; there was very little general weakness. The patient responded only partially to prostigmine.

She had no cardiac symptoms. Examination of the heart was negative. The orthodiagram showed that the size of the heart was normal. The arterial pressure was 100/60; the venous pressure, 6 cm. of water. The saccharin time was 19 sec.; the ether time, 8 sec. The electrocardiogram showed normal rhythm with sinus arrhythmia, a rate of 65 to 75, a P-R of 0.16, a normal QRS, and upright T waves (normal electrocardiogram).

CASE 3.—J. P., a man of 54, came to the myasthenia gravis clinic in February, 1937, with ptosis of the lids of both eyes which had begun rather suddenly four months before. There was no general weakness. He responded immediately to prostigmine (90 to 120 mg. daily), and, as time went on, needed less and less of the drug; finally, in December, 1938, he was able to give up prostigmine treatment entirely, without any return of his symptoms. He has remained in this complete remission ever since.

He had no cardiac symptoms. Examination, during the remission, showed no cardiac abnormality. The orthodiagram showed no cardiac enlargement. The arterial pressure was 130/85; the venous pressure, 13 cm. of water. The saccharin time was 18 sec.; the ether time, 9 sec. The electrocardiogram showed normal

*The authors are indebted to Dr. Paul D. White and Dr. Henry R. Viets for valuable criticism during the course of this investigation.

rhythm, a rate of 70, slight left axis deviation, a P-R of 0.15 sec., normal T waves, and a normal Lead IV (normal record).

CASE 4.—F. L., a woman of 46, came to the hospital in November, 1938, with a five months' story of fatigability, ptosis of the lids of both eyes, general weakness, and difficulty in chewing and talking. She was given prostigmine (60 to 75 mg. daily) and 2.125 Gm. of guanidine hydrochloride, with good results.

She had been breathless on undue exertion since the age of 21 and had occasional dyspnea at night; these symptoms were associated with her general weakness. In one attack she felt that her heart was stopping; occasionally she had nocturnal palpitation. Examination of the heart was negative. The orthodiagram showed no cardiac enlargement. The arterial pressure was 130/85, the venous pressure, 11 cm. of water. The lobeline time was 7 sec.; the ether time, 4½ sec. The electrocardiogram showed normal rhythm, a rate of 78, a P-R of 0.15 sec., upright T waves, and slight right axis deviation (normal record).

CASE 5.—S. V., a woman of 19, came to the hospital in October, 1937, at the age of 17, complaining of difficulty in speaking and swallowing, weakness, and fatigue, of one and one-half years' duration. She has taken as much as 400 mg. of prostigmine daily since 1937, with definite improvement.

When excessively tired, she has had dyspnea in association with her general weakness. She has also been waked up at night, occasionally, when she has not taken her medicine. On examination, her heart was normal. The orthodiagram showed no cardiac enlargement. The arterial pressure was 105/70; the venous pressure, 9 cm. of water. The saccharin time was 14 sec.; the ether time, 6 sec. The electrocardiogram showed normal rhythm, a rate of 95, a P-R of 0.15 sec., and upright T waves (normal electrocardiogram).

CASE 6.—H. C., a man of 45, first came to the hospital in October, 1937, complaining of weakness of his hands, double vision, and some difficulty in chewing and swallowing, of two years' duration. He is now taking 75 to 90 mg. of prostigmine daily, with good results.

He has had no cardiac symptoms. Examination of the heart was negative. The orthodiagram showed no cardiac enlargement. The arterial pressure was 105/70; the venous pressure, 10 cm. of water. The lobeline time was 13 sec.; the ether time, 7 sec. The electrocardiogram showed normal rhythm, a rate of 80, a P-R of 0.16 sec., and slight elevation of R-T in Leads I and II (normal record).

CASE 7.—M. K., a 19-year-old woman, came to the hospital in March, 1935, because of five months of difficulty in speaking and swallowing. She has taken, since 1937, 120 to 160 mg. of prostigmine daily, with excellent results.

She had no cardiac symptoms or signs. The orthodiagram showed that the heart was not enlarged. The arterial pressure was 120/80; the venous pressure, 12.5 cm. of water. The lobeline time was 18 sec.; the ether time, 9 sec. The electrocardiogram showed normal rhythm, a rate of 80, a P-R of 0.16 sec., a normal QRS, upright P waves, and slight right axis deviation (normal record).

CASE 8.—J. B., a 22-year-old man, came to the hospital in 1932 with a complaint of general weakness, particularly in his legs and arms. During the last three years he has been taking prostigmine (250 to 300 mg. daily), with the result that his symptoms have disappeared.

He had palpitation shortly after the onset of his myasthenia and tachycardia with the least excitement, but he has no cardiac symptoms now. Examination of the heart was negative. The orthodiagram showed no cardiac enlargement. The arterial pressure was 105/80; the venous pressure, 14 cm. of water. The lobeline time was 27 sec.; the saccharin time, 25 sec.; and the ether time, 15 sec. The

electrocardiogram showed sinus arrhythmia, a rate of 80 to 60, a P-R of 0.14 sec., normal P waves, upright T waves, and normal QRS complexes (normal record).

CASE 9.—J. H., a man of 56, came to this hospital in June, 1939, with a story of palpebral ptosis of four months' duration, and marked difficulty in swallowing, talking, and chewing of three weeks' duration. He was given prostigmine (150 mg. daily), with marked improvement in his general condition.

He has had no cardiac symptoms. Examination of the heart was negative. The orthodiagram showed no cardiac enlargement. The arterial pressure was 140/90; the venous pressure, 10.5 cm. of water. The lobeline time was 18 sec.; the ether time, 8 sec. The electrocardiogram showed normal rhythm, a rate of 75, a P-R of 0.15 sec., upright T waves in Lead II, and slight left axis deviation (normal record).

CASE 10.—C. L., a 24-year-old man, entered the hospital in July, 1939, with a complaint of general weakness, fatigue in chewing and swallowing, and transient diplopia of eighteen months' duration. He was given prostigmine (120 to 135 mg. daily), with alleviation of his symptoms.

He has had no cardiac symptoms. Examination of the heart was negative. The orthodiagram showed no enlargement of the heart. The arterial pressure was 120/80; the venous pressure, 10 cm. of water. The lobeline time was 18 sec.; the ether time, 9 sec. The electrocardiogram showed normal rhythm, a rate of 72, a P-R of 0.14 sec., normal QRS complexes, and upright T waves in all leads (normal record).

CASE 11.—S. S., a woman of 49, came to the hospital in 1937, complaining of general weakness and ptosis of the lids of both eyes which began in 1933. Since 1937 she has been taking prostigmine (120 mg. daily), with general improvement. She had rheumatic fever in childhood, as a result of which she was kept in bed for some time. She is an extremely neurotic patient, with severe osteoarthritis of one hip.

She had had no definite cardiac symptoms, but there had been signs and symptoms of bronchitis during the preceding few weeks. Examination of the heart was negative. The orthodiagram showed no enlargement of the heart. The arterial pressure was 140/100; the venous pressure, 17 cm. of water. The saccharin time was 19 sec.; the ether time, 7 sec. The electrocardiogram showed normal rhythm, a rate of 75, a P-R of 0.15 sec., upright T waves in all leads, and no abnormal axis deviation (normal record).

CASE 12.—E. H., a 27-year-old woman, came to this hospital in March, 1932, with a story of difficulty in speaking and swallowing, and bilateral palpebral ptosis which began gradually five months previously. She was given prostigmine (120 to 160 mg. daily) in January, 1937, with marked improvement in her symptoms.

She had had occasional attacks in which she felt that she was unable to breathe and was going to die, but these occurred only when she was without medicine. Examination of the heart was negative. The orthodiagram showed that the size of the heart was normal. The arterial pressure was 125/80; the venous pressure, 9 cm. of water. The saccharin time was 13 sec.; the ether time, 7 sec. The electrocardiogram showed normal rhythm, a rate of 75, a P-R of 0.15 sec., upright R waves in Leads I and II and T waves in Lead II, inversion of all waves in Lead III, and slight left axis deviation (normal electrocardiogram).

CASE 13.—W. D., a man, 66 years of age, was referred to this hospital in November, 1938, because of ptosis of the lids of both eyes, double vision, general weakness, and difficulty in chewing, swallowing, and talking of six months' duration. He was given prostigmine by mouth (150 mg. daily), and is doing well.

He had no cardiac symptoms, but was known to have had hypertension for a few years. Examination showed that he was apparently a healthy man, with no enlargement of the heart. The heart sounds were not remarkable; the aortic second sound was louder than the pulmonic second. The blood pressure was 166/96. The electrocardiogram was normal; it showed normal rhythm, a rate of 75, notched P waves in Leads I and II, and a flat T_3.

CASE 14.—S. S., a 64-year-old woman, came to the myasthenia gravis clinic in May, 1937, with intermittent palpebral ptosis of almost nine years' duration. She was given prostigmine (90 to 120 mg. daily) and is somewhat improved.

She has had breathlessness, when working and walking, for two years, but she has had no nocturnal dyspnea and is able to sleep without extra pillows. She is known to have had hypertension for ten years. Examination showed a palpable thyroid gland, but no definite signs of hyperthyroidism. Fluoroscopic examination showed enlargement of the heart, especially of the left ventricle. The heart sounds were normal, and the blood pressure was 185/105. The electrocardiogram showed normal rhythm, a rate of 80, a P-R of 0.14 sec., notching of QRS in Lead III, and a variable T_3 (normal record).

SUMMARY OF CARDIAC EXAMINATIONS

Examination of the heart has shown no abnormalities in this group of fourteen patients with myasthenia gravis. Some patients, as in Cases 4, 5, and 11, have had some difficulty in breathing when they are not taking prostigmine. Others, as in Case 4 and Case 8, have had occasional attacks of palpitation. Inasmuch as we carried out our examinations when the patients were not being treated, and could then find no abnormalities, we believe that there is no justification for attributing these symptoms to any disturbance in the myocardial function; they are more likely the result of the general weakness and nervousness engendered by the disease.

In Case 11, the patient had a rather high venous pressure and a slightly elevated diastolic arterial pressure when she was first examined. We think that the bronchitis which was present was sufficient to account for these slight abnormalities. When she was examined two months later, she appeared well.

In Case 12, the patient complained of occasional attacks of dyspnea, one of which we had the opportunity to observe. Following the measurement of the circulation time, she developed marked bradycardia and a drop in the blood pressure, accompanied by dizziness. The attack was quickly relieved by adrenalin. Similar attacks were produced by carotid sinus compression, proving that there was an increase of vagal activity; this was evidence against the possibility of any myasthenic involvement of the heart.

In Cases 13 and 14 there was slight elevation of the arterial blood pressure; this had been known for many years. There had been no apparent change with the onset of myasthenia gravis. This fact also suggests that the heart is not involved in this disease.

EFFECT OF VAGUS STIMULATION IN PATIENTS WITH MYASTHENIA GRAVIS

Inasmuch as myasthenia gravis has been thought to be caused by dysfunction of the action of acetylcholine at the myoneural junction, it was of interest to ascertain whether the vagus nerve was exerting its normal control on the heart. Therefore, we tested the effect of carotid sinus pressure, mecholyl, and atropine on all fourteen patients. The results are given in Table I.

Carotid Sinus Pressure.—The carotid sinus reflex was tested in all fourteen patients, and was active in ten. The decrease in the heart rate varied from fifteen to twenty-five beats per minute. In three other patients there was extreme slowing, i.e., to thirty-five or forty beats per minute, and, in the remaining patient (Case 12), complete S-A block was produced momentarily.

Mecholyl.—The effects of mecholyl were studied in ten patients. Nine patients were under treatment with prostigmine, a drug which is synergistic with mecholyl, although at the time of the test the drug had been withdrawn long enough to allow the development of myasthenic symptoms. For these reasons, only small doses of mecholyl were administered, namely, 10 to 15 mg. The drug was injected subcutaneously under basal conditions; electrocardiograms and blood pressures had been recorded previously. Immediately after the injection the electrocardiogram was recorded continuously, the blood pressure was taken, and any symptoms were noted. Because of their difficulty in swallowing, the salivation produced by mecholyl caused some patients much discomfort. In all cases a marked tachycardia and fall of blood pressure were noted. The tachycardia started about thirty seconds after the injection, attained its maximum after three minutes, on the average, and remained at a constant rate for approximately ten minutes. The maximum fall in blood pressure also occurred within about thirty seconds; the pressure then gradually returned to normal, before the heart rate. Even when the decrease in blood pressure preceded the tachycardia, there was no direct relationship between them.

In four cases, the electrocardiograms showed, in addition to the sinus tachycardia, slight prolongation of the P-R interval (from 0.02 to 0.04 second). There were only a slight depression of the S-T segment in three cases and slight or definite flattening of the T waves in four cases. These changes in the ventricular complexes were closely related to the tachycardia in all cases. In addition to the cardiovascular symptoms, the patients had marked sweating, which developed within five minutes, and profuse salivation; some had nausea, and one had vomiting. In five cases an injection of 1.5 mg. of atropine was necessary in order to stop the mecholyl symptoms. These cases were those in which prostigmine had been omitted only a comparatively short time before.

The signs and symptoms produced by mecholyl in this group of patients were essentially similar to those which occur in normal subjects.

TABLE I

RESULTS OF TESTS WITH MECHOLYL AND ATROPINE

CASE NUMBER	1	2	3	4	5	6	7	8	9	10	11	12	13	14
SEX	F	F	M	F	F	M	F	M	M	M	F	F	M	F
AGE	19	26	54	46	19	42	19	22	56	24	49	32	66	64
Daily Dose of Prostigmine in mg.	60	100	0	75	400	90	160	300	150	120	120	160	150	120
Hours Since Last Medication	8	8		10	10	10	4	8	8	15	5	12	4	8
Resting Pulse Rate	85	75	80	80	80	70	80	80	75	75	75	75	75	80
Blood Pressure	120/80	100/60	130/85	130/85	105/75	105/70	120/80	105/80	140/90	120/80	140/100	125/80	166/96	185/105
Mecholyl (mg.)	10	10	15	10	10	10	10	10	10	10				
Drop in B.P. (mm. Hg)	30	5	10		15	9	60	15	15	18				
Time to fall (sec.)	30	30	120	45	60	45		45	60	30				
Time to return to normal (min.)	17	2	5	8		6		9	6	20				
Maximum tachycardia	160	150	100	140	150	100	140	135	120	140				
Time to attain maximum (min.)	6	2	3	8	1.75	2	3	8	3	5				
Time of onset of tachycardia (sec.)	15	30	60	60		0	30	30	60	30				
Atropine (gr.)	1/50	1/50	1/50	1/50	1/50	1/50	1/50	1/50	1/50	1/50	1/50	1/50		1/50
Maximum tachycardia	160	120	90	125	125					120	120	140		125
Time to attain maximum (min.)	16	20	10	15	20					15	15	20		15
Atropine for severe reactions		Yes			Yes		Yes	Yes	Yes					

Any difference that was noted was regarded as a result of the nervous reactions following the discomfort caused in these myasthenic patients. The marked response in the four cases in which prostigmine medication had been omitted for only a few hours may have been caused, in part, by summation of the two drugs. As Dameshek, et al.,[11] have shown, when small doses of mecholyl are given after the administration of prostigmine, a marked effect is produced. The fact that these patients were not taking prostigmine at the time of the test is no proof that all of the drug had been eliminated.

It is not the purpose of this paper to discuss the tachycardia that normally follows the injection of mecholyl, but, judging from the results which were obtained, we believe, as Dameshek does, that the fall in blood pressure is not the only factor in the production of the tachycardia.

Atropine.—The effect of atropine was studied on nine patients. One-fiftieth grain was given subcutaneously in every case, at a time when the patients were not taking prostigmine. As in the case of mecholyl, the electrocardiogram and blood pressure were recorded. In all of the cases tachycardia appeared approximately three minutes after the administration of atropine and reached a maximum after fifteen minutes. No definite alteration in blood pressure accompanied the changes in heart rate. The electrocardiogram showed, in addition to the sinus tachycardia, slight shortening (0.02 second) of the P-R interval in six of the eight patients. Only a slight depression of the S-T segment occurred in two cases, and slight flattening of the T waves in two other cases. The reactions to atropine, as well as to mecholyl, of patients with myasthenia gravis are the same as those of normal subjects.

POST-MORTEM EXAMINATION OF PATIENTS WITH MYASTHENIA GRAVIS

Post-mortem examination in cases of myasthenia gravis has been reported as showing lymphocytic infiltration in all muscles, but, in general, the heart has been considered normal. Barton and Branch[9] found marked lymphocytic infiltration in one case in which there had been marked myasthenia gravis symptoms and a high basal metabolic rate.

We had the opportunity of performing a post-mortem examination in one of our cases (Case 2); the patient died from bronchopneumonia and massive collapse of the lung. Histologic and gross examination of the heart showed nothing abnormal. In addition, re-examination of the hearts of two patients with myasthenia gravis who had died previously at the Massachusetts General Hospital disclosed no abnormalities.

CONCLUSIONS

1. The cardiovascular systems of fourteen patients with myasthenia gravis of varying duration and severity were studied.

2. Clinical examination of the cardiovascular system was negative in all cases.

3. The carotid sinus reflex was active in every case.

4. The reaction to the subcutaneous injection of 10 to 15 mg. of mecholyl was the same as that which occurs in normal subjects.

5. The reaction to the administration of $\frac{1}{50}$ grain of atropine was also normal.

6. Post-mortem gross and histologic study of one of these patients, as well as of two others at the Massachusetts General Hospital, showed no cardiac abnormality.

REFERENCES

1. Willis, Thomas: De Anima Brutorum, London, 1672, p. 288.
2. Erb, Wilhelm: Zur Casuistik der bulbaren Lähmungen: 3, Ueber einem neuen, wahrscheinlich bulbaren Symptomencomplex, Arch. f. Psychiat. **9**: 336, 1878.
3. Goldflam, S.: Ueber einem scheinbar heilbaren bulbarparalytischen Symptomencomplex mit Betheiligung der Extremitäten, Deutsche Ztschr. f. Nervenh. **4**: 312, 1893.
4. Jolly, F.: Pseudoparalysis Myasthenica, Neurol. Centralbl. **14**: 34, 1895; Myasthenia Gravis Pseudoparalytica, Verhandl. d. Berl. med. Gesellsch. **25**: 249, 1895.
5. Boothby, W. M.: Myasthenia Gravis: Eighth Report, Tr. A. Am. Physicians **51**: 188, 1936.
6. Kennedy, F. S., and Moersch, F. P.: Myasthenia Gravis: A Clinical Review of Eighty-Seven Cases Observed Between 1915 and the Early Part of 1932, Canad. M. A. J. **37**: 216, 1937.
7. Viets, H. R., and Schwab, R. S.: The Diagnosis and Treatment of Myasthenia Gravis With Special Reference to the Use of Prostigmine, J. A. M. A. **113**: 559, 1939.
8. Lange, Sidney: Personal Communication.
9. Barton, F. E., and Branch, C. F.: Myasthenia Gravis: Report of Case With Necropsy, J. A. M. A. **109**: 2044, 1937.
10. Burwell, C. S., Lyons, R. H., and Kennedy, J. A.: The Measurement of Venous Pressure by the Direct Method, Am. Heart J. **16**: 675, 1938.
11. Dameshek, W., et al.: Human Autonomic Pharmacology; Effect on Normal Cardiovascular System of Acetyl-Beta Methylcholine Chloride, Atropine, Prostigmin, Benzedrine—With Especial Reference to Electrocardiogram, Am. J. M. Sc. **195**: 88, 1938.

THE EFFECT OF THE INTRAVENOUS ADMINISTRATION OF QUINIDINE SULFATE ON THE DEVELOPMENT OF VENTRICULAR FIBRILLATION FOLLOWING SUDDEN OCCLUSION OF THE CIRCUMFLEX BRANCH OF THE LEFT CORONARY ARTERY

An Experimental Study

F. H. Smith, M.D., C. G. McEachern, M.D.,
and G. E. Hall, M.D., Ph.D.
Toronto, Can.

SUDDEN occlusion of an important branch of a coronary artery results in a characteristic sequence of events which may terminate in fatal ventricular fibrillation.

There is a remarkable similarity between the symptoms exhibited by an animal dying of ventricular fibrillation and those of a man dying suddenly of coronary occlusion; in both cases, there are cyanosis, pallor, venous congestion, gasping respirations, loss of pulse pressure, and a sudden loss of consciousness, followed by death.

In the majority of cases in which death occurs suddenly as a result of ventricular fibrillation, autopsy reveals a coronary lesion, usually in the form of sclerosis. That the presence of coronary sclerosis triples the incidence of sudden death from coronary thrombosis has been shown by Levy's[1] study of a large group of cases. There is also a relationship between sclerosis of the coronary arteries and ventricular fibrillation, for in the majority of cases in which death occurs suddenly as a result of ventricular fibrillation autopsy reveals such lesions.

At the present time the number of cases in which the mechanism of the dying heart has been recorded by the electrocardiograph is relatively small. Similar records in cases of "sudden" death are quite rare. However, in the majority of these cases death was caused by ventricular fibrillation. Although one or two instances of survival have been recorded, most patients die suddenly once true ventricular fibrillation becomes established.

Several theories which have been advanced as to the cause of sudden cardiac death will be discussed in detail in a subsequent paper. At this time only experimental ventricular fibrillation will be considered. As early as 1850, Hoffa and Ludwig[2] recognized ventricular fibrillation, produced by electrical stimulation, as a cause of death in animals. Death produced in animals by chemical, mechanical, and various other means is also, in most cases, the result of ventricular fibrillation. Some-

From the Department of Medical Research, Banting Institute, University of Toronto.
Aided in part by a grant from the Josiah Macy, Jr., Foundation, New York.
Received for publication March 7, 1940.

what more comparable to the clinical condition which leads to ventricular fibrillation and sudden death is the experimental occlusion of a major branch of a coronary artery in the conscious animal.

Many drugs, with entirely different properties, have been employed in the past in the treatment of cardiac irregularities. One of these drugs, quinidine sulfate, has been used widely as a preventive of auricular and ventricular tachycardia, as well as in the treatment of these ectopic rhythms once they become established. Its use has also been advocated for the treatment of auricular fibrillation. Hepburn and Rykert[3] reported twenty-six cases of ventricular tachycardia, in nine of which quinidine sulfate was given intravenously. They concluded "that intravenous quinidine sulfate may be a life-saving drug in ventricular tachycardia." Morawitz and Hochrein[4] regarded quinidine sulfate as a highly successful prophylactic in the treatment of patients who were liable to sudden cardiac death from ventricular fibrillation, and Stepp and Parade[5] advocated its use as a means of preventing fibrillation.

Quinidine sulfate abolishes vagal tone, thus lengthening the refractory period of auricular muscle and decreasing the transmission rate of the nervous impulse. It also acts directly on the ventricular and auricular myocardium, lengthening the refractory period and slowing the rate of conduction. Furthermore, it decreases conduction time in the junctional tissue.

That these actions are not always specific has been shown by the fact that cases of auriculoventricular block, extrasystoles, paroxysmal tachycardia, and even fatal ventricular fibrillation have been reported as a result of using large doses of this drug in the treatment of heart disease. It has been suggested that the development of ventricular fibrillation is caused by the establishment of circus movements in the ventricle, and that the latter result from a greater reduction in the rate of conduction in the ventricular myocardium than lengthening of the refractory period.

Since quinidine sulfate is an important drug clinically, it was thought advisable to study its effects on the development of the ventricular tachycardia and ventricular fibrillation which are produced experimentally by coronary artery ligation in conscious animals. The purpose of this paper is to present the results of such a study.

EXPERIMENTAL PROCEDURE

Normal, healthy dogs which weighed approximately 6.5 kg. were used. Electrocardiograms were taken before operation, before and after drug administration, and at various intervals following ligation.

The heart was exposed through the left fourth intercostal space. After careful dissection of the circumflex branch of the left coronary artery, a loose ligature was placed around the vessel in the manner previously described.[6] Sufficient ligature was left in the chest to allow for lung expansion without causing tension

on the loosely tied knot, and the loose ends were led from the chest via the wound. The chest was then closed as tightly as possible, and a sterile collodium dressing applied.

In all cases, intratracheal ether anesthesia was given following the subcutaneous administration of one-quarter grain of morphine sulfate.

When the animal had completely recovered from the effects of the anesthetic, i.e., in approximately twenty-four hours, it was carefully carried from its cage, in order to avoid unnecessary excitement, and a second electrocardiogram taken. Quinidine sulfate, in relatively large doses (32.5 mg./kilo.), was then given slowly by intravenous injection. Further electrocardiograms were taken.

The effects of the drug were not uniform. Distress was evidenced by muscular twitching, which was usually followed by a severe convulsion. The convulsion was accompanied by marked dyspnea, cyanosis of oral mucous membranes, salivation, and, frequently, by vomiting. Most of these symptoms could be avoided if the drug was given very slowly, but in some animals the rate of injection or the amount given was apparently not related in any way to the resultant distress.

Ten minutes after the administration of the drug, coronary occlusion was produced by traction on the extrathoracic ends of the ligature. Very little, if any, pain was experienced by the animal when the artery was ligated.

The various electrocardiographic changes which occurred were then recorded (Lead II) until the animal either died or acted as if it would survive. In these latter cases, electrocardiograms were taken at various intervals for several days.

Twenty animals were used in this series. Of this number, eleven, or 55 per cent, died within twenty-four hours. Nine of these eleven animals died, however, within five minutes of the ligation.

ELECTROCARDIOGRAPHIC CHANGES

In all cases, the quinidine sulfate produced a definite acceleration of the heart rate (Fig. 1 *B*). In a few instances, however, isolated extrasystoles were also observed. Within two or three seconds of ligation many extrasystoles appeared, and, within ten seconds, the normal ventricular complexes had been replaced by long runs of ventricular extrasystoles. Almost immediately, ventricular tachycardia became well established.

In the animals which eventually recovered, the stage of ventricular tachycardia was usually maintained for some time (Fig. 1 *F*). After this stage, the ventricular complexes became quite irregular in shape, rate, and amplitude. There followed a progressive decrease in the amplitude of the ventricular complex, together with better definition of the R-T segment (Fig. 1 *H*). At the same time, the beating became progressively more regular, until, after about thirty minutes (Fig. 1 *I*), both the auricular and ventricular complexes were approximating the normal. The axis deviation which is typically associated with occlusion of the circumflex branch of the left coronary artery developed within the next few days.[6] Within eighteen to twenty-four days the electrocardiogram was essentially normal (Fig. 1 *J*).

The electrocardiograms of the animals which did not survive likewise showed a rapid elevation of the R-T segment, a high take-off of the T wave, a marked increase in the amplitude of the waves, and an early

absence of P waves (Fig. 2). Usually, the rate was considerably accelerated. The early ventricular tachycardia was soon folowed by a more rapid type, with waves of great amplitude (Fig. 2 *D*), which rapidly passed into the stage of true ventricular fibrillation (Fig. 2 *E*). Fatal ventricular fibrillation in these cases almost always developed within ninety seconds of ligation.

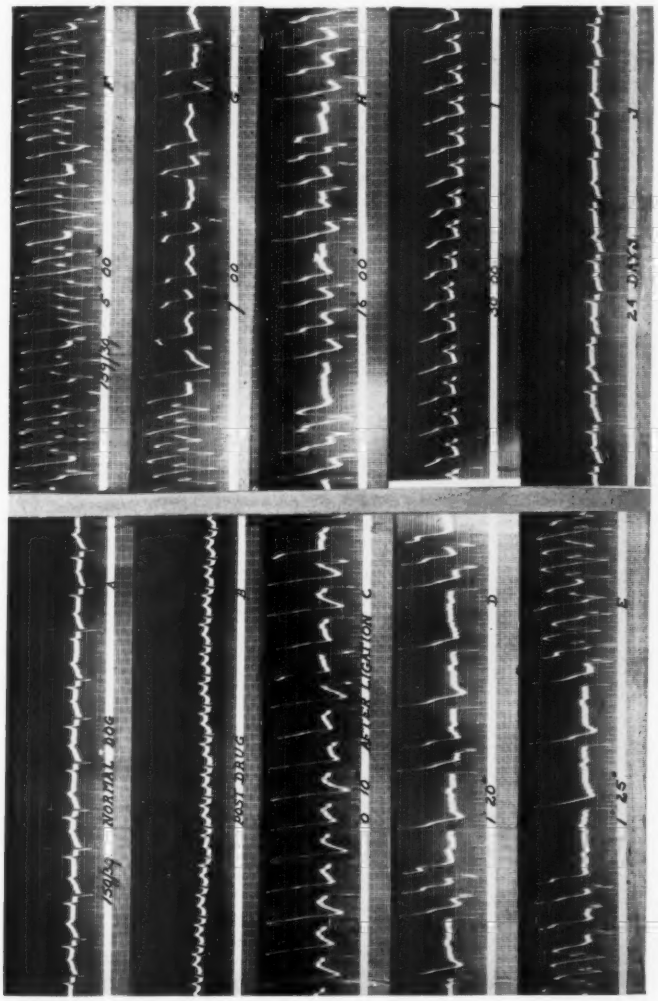


Fig. 1.—Lead II, showing progressive changes following ligation of the circumflex branch of the left coronary artery of a dog treated with quinidine sulfate. Note early onset of gross cardiac irregularities and immediate rise of the R-T segment.

COMMENTS

In these experiments quinidine sulfate was used in relatively large doses so that a maximal effect could be observed. This dose, however, was not grossly out of proportion to that which has been used clinically.[3]

The effect of intravenously injected quinidine sulfate is to quicken the heart rate; this acceleration may or may not be associated with occasional ventricular extrasystoles.

There are significant differences between the electrocardiograms of an animal which has been previously treated with quinidine sulfate, and a normal, untreated animal, following ligation of the circumflex branch of the left coronary artery. The sequence of events in the latter is a progressive rise in the R-T segment, extrasystoles, and ventricular tachycardia, which in most cases is followed by ventricular fibrillation (Fig. 3). When ventricular tachycardia becomes well established in animals which did not receive quinidine sulfate, it is practically always followed by fatal ventricular fibrillation. However, in an animal which has been treated with quinidine sulfate, ventricular tachycardia is apparently much more easily initiated and occurs more frequently, but the number of recoveries once the tachycardia becomes well established is much larger than in untreated animals.

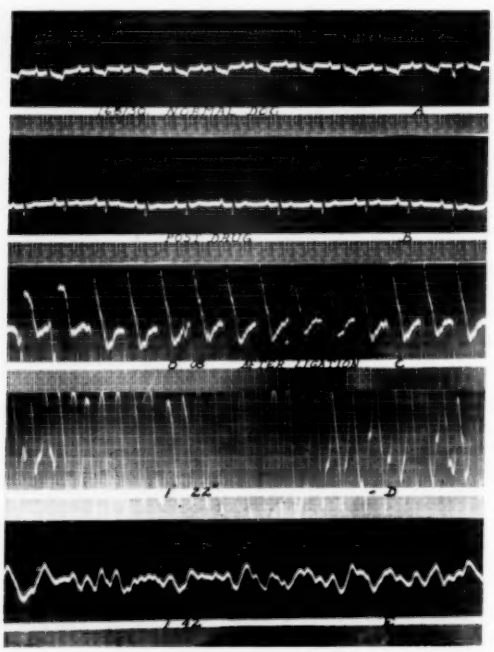


Fig. 2.—Lead II, showing changes preceding fatal ventricular fibrillation in a quinidine-treated animal. Note early cardiac irregularities, with rapid onset of ventricular tachycardia.

Examination of the electrocardiogams indicates that, after the intravenous injection of quinidine sulfate and subsequent coronary ligation, the myocardium is more sensitive to the establishment of ectopic foci, with the result that marked irregularities occur. Extrasystoles from many foci and ventricular tachycardia were frequently observed. Although recovery from these serious disturbances in the cardiac mechanism was more frequent than in untreated animals, and the mortality was lowered somewhat (from about 75 per cent to 55 per cent), it would

appear that quinidine sulfate is of little use in the preventive treatment of disordered mechanisms caused by experimental occlusion of coronary arteries. Indeed, it hastens their onset.

However, quinidine sulfate does abolish almost completely the cardiac pain so characteristically experienced by conscious dogs after ligation of a main branch of a coronary artery. The afferent pain pathways from the heart thus appear to have been depressed by this drug. This suggests that pain pathways are separate from those which produce fibrillation reflexly.

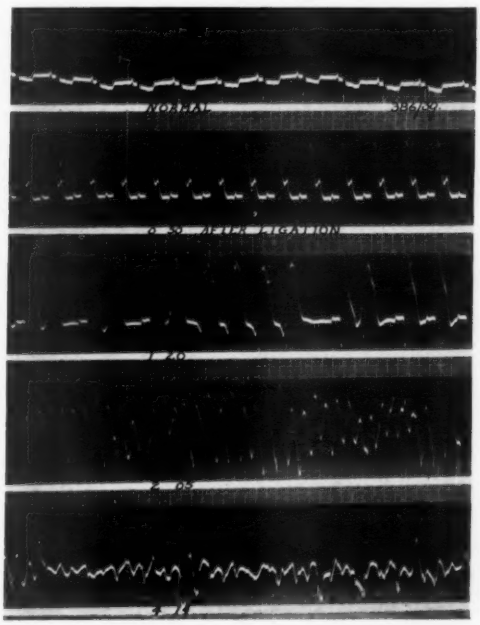


Fig. 3.—Lead II, showing progressive changes preceding fatal ventricular fibrillation in a normal, conscious dog, following ligation of the circumflex branch of the left coronary artery. Note gradual build-up of the R-T segment.

Fig. 4.—Lead II, showing sudden change of foci initiating extrasystoles from right to left ventricular myocardium.

The electrocardiograms also show that, although it was the circumflex branch of the left coronary artery that was ligated, the majority of the foci which initiated the extrasystoles and tachycardia were located in the right ventricle. However, in some instances there was a sudden shift of foci from the right ventricle to the left, as shown in Fig. 4. Also, the

form of the extrasystoles was not the same in every case, indicating that the foci which were initiating the irregularities must have been continually shifting their positions in the ventricular myocardium.

SUMMARY

1. Quinidine sulfate depresses the cardiosensory mechanism in dogs. This suggests that pain pathways are separate from those which produce fibrillation reflexly.

2. Quinidine sulfate renders the dog's myocardium more susceptible to the development of cardiac irregularities. Extrasystoles of left, as well as right, ventricular origin were recorded.

3. Quinidine sulfate lowers, to some extent, the mortality caused by coronary occlusion in dogs. In twenty animals the mortality was 55 per cent, as compared to 75 per cent in a control series.

REFERENCES

1. Levy, R. L.: Sudden Death in Patients With Coronary Sclerosis and Thrombosis, Tr. Am. Climat. and Clin. A. **51**: 85, 1935.
2. Hoffa, M., and Ludwig, C.: Einige neue Versuche ueber Herzbewegung, Ztschr. f. rat. Med. **9**: 107, 1850.
3. Hepburn, J., and Rykert, H. E.: The Use of Quinidine Sulfate Intravenously in Ventricular Tachycardia, AM. HEART J. **14**: 620, 1937.
4. Morawitz, P., and Hochrein, M.: Zur Verhütung des akuten Herztodes, München. med. Wchnschr. **76**: 1075, 1929.
5. Stepp, W., and Parade, C. W.: Untersuchungen und Betrachtungen über den plötzlichen Herztod durch Kammerflimmern, München. med. Wchnschr. **75**: 1869, 1928.
6. Manning, G. W., McEachern, C. G., and Hall, G. E.: Reflex Coronary Artery Spasm Following Sudden Occlusion of Other Coronary Branches, Arch. Int. Med. **64**: 661, 1939.

Department of Clinical Reports

LEFT AURICLE WITH A CAPACITY OF 1,695 GRAMS OF BLOOD IN A CASE OF MITRAL STENOSIS

ROBERT LYMAN NELSON, M.D.
DULUTH, MINN.

IN 1931, Bland, Balboni, and White[1] reported a case of "Enormous Increase of Heart Volume With Mitral Stenosis," and noted the paucity of volumetric data in such cases. They described a heart which weighed 4,600 grams when filled, with the pericardium attached, and 850 grams when emptied and stripped in the usual manner. The left auricle held 1,760 grams of fluid and the right auricle 660 grams; the latter was the largest figure on record. Only three other cases[2, 3, 4] were found in which the left auricular capacity was larger. Although numerous reports of massive enlargement of the left auricle have appeared since that time, I have found no case in which the capacity equalled that in those four or in the additional case herein reported.

CASE REPORT

E. P., a man, aged 28, was admitted to the medical service of the Miller Memorial Hospital on Sept. 18, 1939, with complaints of dyspnea, orthopnea, edema of the legs, ascites, and weakness. He had had heart trouble as long as he could remember; even in childhood his activities were limited. Two years earlier he had had his first attack of congestive heart failure. He improved after five weeks in bed, and quite comfortably engaged in light work until two months before admission, when he was forced by increasing shortness of breath to go to bed. General circulatory failure ensued, and death occurred Sept. 23, 1939.

In early childhood he had had chorea and occasional attacks of tonsillitis. There was no history of rheumatic fever or scarlet fever. There had been frequent nosebleeds during childhood and two during the preceding week. Swelling of the lower extremities below the knees had been present in varying degrees for many years.

Examination revealed a well-developed and fairly well-nourished white man who appeared to be about 25 years of age. He was alert, but conserved all possible energy by lying quietly. He breathed with considerable effort. The neck veins were markedly distended. The thorax was of the "pigeon breast" type, with a depth approximately equal to the width; the excursion was limited, and the breath sounds were obscured by roaring heart sounds. Complete dullness extended below the fourth intercostal space. The heart was completely irregular, and the rate was about 70 beats per minute. The apex impulse was diffuse, and extended low in the left anterior axillary line. There was a systolic retraction of the precordial intercostal spaces. A systolic roar and a less intense diastolic murmur were heard over the entire chest. The blood pressure was approximately 118/80.

The liver extended to the level of the umbilicus. It was pulsating, hard, and tender. Ascites, with shifting dullness in the flanks, was noted. There was considerable edema of the scrotum and extremities.

Received for publication Dec. 11, 1939.

Laboratory Data.—The urine contained albumin (three plus) and numerous hyaline casts. The hemoglobin was 13 grams, the erythrocyte count, 4,230,000, and the leucocyte count, 5,950, with a differential count of 62 per cent polymorphonuclears, 35 per cent lymphocytes, and 3 per cent large mononuclears. The blood Wassermann reaction was negative. An electrocardiogram showed auricular fibrillation, right

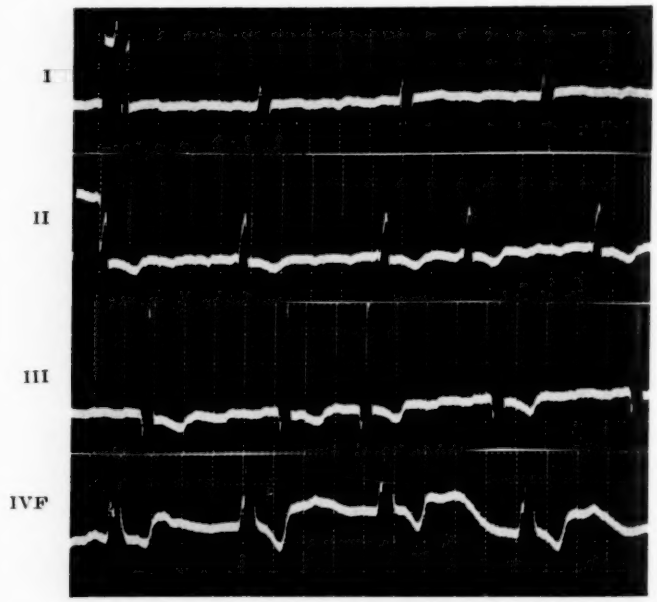


Fig. 1.—Electrocardiogram taken Sept. 18, 1939, five days before death. It shows auricular fibrillation, right axis deviation, low T_1 and inversion of T in II, III, and IVF. Lead IVF is international IVF.

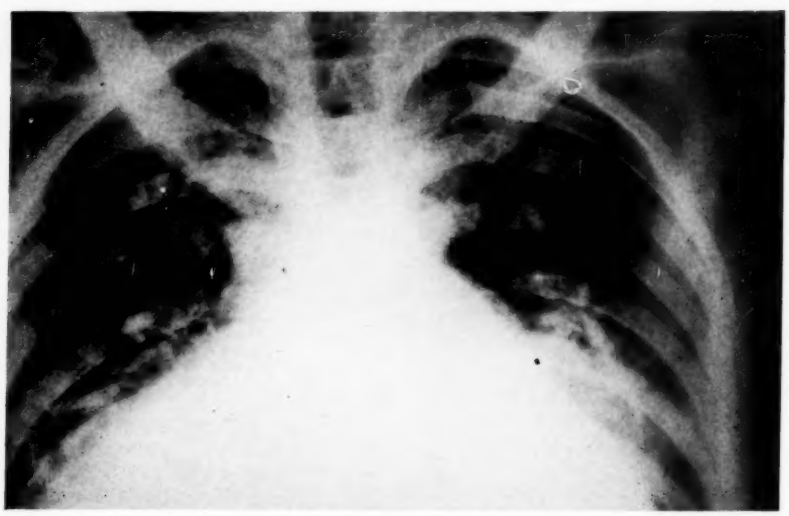


Fig. 2.—This roentgenogram was taken at a 35-inch tube distance. It shows the enormous, smoothly rounded left auricle extending to the right chest wall. There was relatively little distortion of the size, shape, and position of the heart, as ascertained by clinical methods.

axis deviation, and abnormal S-T segments (Fig. 1). A roentgenogram of the chest (Fig. 2) showed a massive heart shadow and some congestion of both lungs.*

The patient's course during the short period of hospitalization was unsatisfactory. No benefit was obtained from digitalization and dehydration with salyrgan. Oxygen gave temporary relief, and, together with small doses of morphine, maintained an extraordinary degree of comfort. Death occurred at 5:15 A.M. on Sept. 23, 1939, and was not actually observed. A short time before, the floor nurse reported that the patient was sleeping quietly and breathing fairly easily.

The autopsy was performed by Dr. G. L. Berdez, clinical pathologist to St. Mary's Hospital, Duluth. Many details which are not pertinent will be omitted.

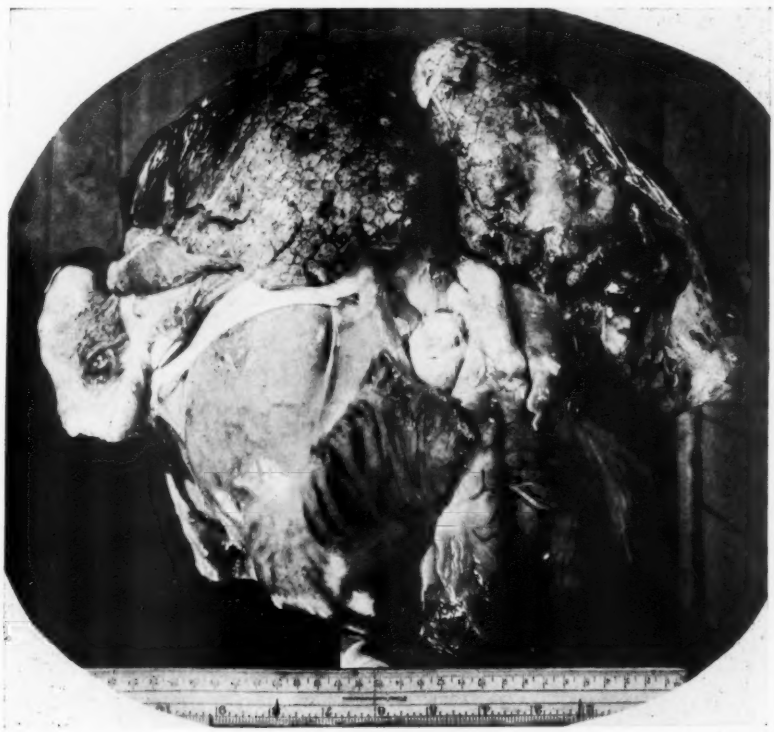


Fig. 3.—Anterior view of the excised heart and lungs immediately after removal. The lungs and the reflected pericardium lie at the upper portion. The ventricles are at the lower right, with left auricular appendage at the upper end of the interventricular sulcus. The left auricle occupies the large area to the left of the ventricles and basal vessels, and shows a surface which is partly muscular and mostly smooth and shiny.

The body was emaciated (grade II). There were innumerable petechiae in the skin, mainly over the shoulders, thighs, and chest. The chest was thicker than it was wide; the transverse diameter was 25½ cm., and the anteroposterior was 27 cm. There was edema below the knees. The peritoneal cavity contained 1,200 c.c. of slightly bloodtinged, straw-colored fluid. The liver extended 1½ cm. below the costal margin in the right midclavicular line. The left half of the diaphragm extended to the fifth intercostal space, and the right to the sixth. The left pleura showed ex-

*A sphygmogram taken on a Cameron Heartometer by Dr. C. M. Smith on July 5, 1939, was interpreted by him as showing a mitral stenosis type of bulging of the descending limb and a few ventricular extrasystoles.

tensive fibrous adhesions, and the right pleura showed a few fibrous adhesions between the lower lobe and the diaphragm, and contained about 40 c.c. of a dark, straw-colored fluid.

The heart occupied the entire lower half of the thoracic cavity; the relative extent of the individual chambers is shown in the photographs of the excised organs (Figs. 3 and 4). The left auricle extended to the right above the right auricle and over the right pulmonary veins. The heart and lungs were removed in toto, and the utmost caution was observed in tying off vessels in order to avoid leakage.* After removal, the specimen was immediately photographed, and then fixed in formalin solution for five days. This was done at the suggestion of Dr. Arthur H. Wells, clinical pathologist to St. Luke's Hospital, Duluth, who also prepared the specimen for display in accordance with his technique (soon to be described under the title of "The Preparation of Pathological Specimens" in the technical supplement of the *J. Am. Soc. Cl. Path.*). The volumetric measurements and gross examination of the fixed heart were made by Doctors Berdez and Wells and the author.

Fig. 4.—Posterior view, showing the massive, cystic appearance of the left auricle.

The weight of the heart filled, but stripped of pericardium, was 3,225 Gm.; the weight empty was 870 Gm.; the weight of the blood in the various cavities, removed separately, was as follows: left auricle, 1,695 Gm., right auricle, 405 Gm., left ventricle, 135 Gm., and right ventricle, 120 Gm. The measurements of the heart

*The care required to remove such a heart intact can be compared with the surgical removal of an ovarian cyst of similar size. Rupture would preclude accurate measurement of the blood content.

after removal, but before opening, were as follows: total length, 33 cm.; left auricle 22 cm. wide, 22 cm. in vertical diameter, and 15 cm. thick. The mitral cusps formed a slit 3.7 cm. long by 0.2 to 0.5 cm. wide. They were partly fused and calcified; the calcification formed a rectangular surrounding mass which was irregular, hard, and rigid, and measured about 2 by 6 cm. (Fig. 5). The tricuspid valve admitted four fingers. The pulmonic valve was normal, and the aortic valve was slightly thickened, but relatively sufficient. The coronary orifices were normal and the arteries themselves in good condition. The foramen ovale was closed; the myocardium was smooth and congested. Both lungs were diffusely congested, as were all of the parenchymatous organs. The adrenals showed but little lipoid, with a rather thick pigment layer and only a moderate amount of medullary substance. The liver showed marked central chronic passive congestion, some fatty change, and an increase in consistency but decrease of fragility. The aorta showed a few yellowish deposits in the intima. There was a middle dorsal kyphosis. Blood in the body cavities coagulated very rapidly.

Fig. 5.—Roentgenogram of the excised heart, showing the calcification about the mitral orifice. Before taking, the heart had been fixed and stuffed with cotton. The different densities of the thin left auricular wall and the other tissues are clearly shown. Calcification about heart valves is seldom visible in roentgenograms of living subjects except when they are taken with a special technique, although it is easily visualized under the fluoroscope in a large percentage of cases.

Microscopic examination of the tissues revealed nothing unusual. The lungs showed marked passive congestion, and the alveoli contained much coagulated albuminous material and numerous erythrocytes; some alveoli contained mononucle-

ated cells loaded with brownish pigment granules (heart failure cells). Some of the alveoli were larger than normal (emphysematous). The kidneys showed distended glomerular loops, and the tubules contained coagulated albuminous material and had a lining cytoplasm which was often slightly granular.

Pathologic Diagnoses:

1. Mitral stenosis and insufficiency, with calcification (grade IV).
2. Hypertrophy and dilatation of the heart.
3. Extreme dilatation of the left auricle.
4. Partial collapse of the lungs (caused by encroachment of the heart).
5. Chronic passive congestion of the lungs, with extensive pleural adhesions.
6. Central chronic passive congestion of the liver.
7. Beginning cardiac cirrhosis of the liver.
8. Ascites.
9. Edema of the legs (two plus).
10. Chronic passive congestion of the spleen.
11. Petechiae in the skin.
12. Terminal hemorrhages in the epicardium and the mucosa of the stomach and intestines.

DISCUSSION

This case is reported for several reasons:

1. The left auricular dilatation, substantiated by volumetric data, is one of the largest on record.

2. A roentgenogram of the chest, although it was not a teleoroentgenogram, helped to visualize the position of the heart in the chest.

3. An electrocardiogram which was taken a few days before death showed what one would expect with such clinical and pathologic findings.

4. The changes are particularly well illustrated by a roentgenogram of the excised organ, which shows the extent of the calcific process about the mitral valve.

The relation between the weight of contained blood and the capacity for water is speculative. Dr. Wells feels that the fixation employed in this case altered the blood weight very little, decreasing it if it changed it at all. It seems probable that more tension would result from filling the heart with water, and that the figure thus obtained would exceed the 1,695 Gm. blood weight.

Such a case impresses one with the remarkable adaptability of the cardiovascular mechanism. The accommodation to gradual changes leads one to speculate on the rationale of obtaining the optimum adaptation when other lesions are present. The pumping action of the enormous auricle was supplanted by an obviously small gravitational flow into the left ventricle, and, to a larger extent, by rhythmic pressure exerted by the diaphragm and accessory muscles of respiration; and, finally, the effectiveness of these was maintained only by the numerous factors which act to maintain vascular tone.

The author wishes to express his appreciation to Dr. Gage Clement and Miss Leve Bergholtz, of the St. Luke's Hospital X-ray Department, for the photographs and roentgenogram.

REFERENCES

1. Bland, Edward F., Balboni, Gerardo M., and White, Paul D.: Enormous Increase of Heart Volume With Mitral Stenosis, J. A. M. A. **96:** 840, 1931.
2. Minkowski, O.: Demonstration eines Herzens mit ungewöhnliche starker Dilatation der Verhofe, München. med. Wchnschr. **51:** 182, 1904.
3. Muller, G.: Ungewöhnliche Dilatation des Herzens und Ausfall der Vorhofsfunction, Ztschr. f. klin. Med. **56:** 520, 1905.
4. Goedel, A.: Eine ungewöhnliche Form der Herzvergrösserung bei mitral Stenose, Wien. klin. Wchnschr. **42:** 427, 1929.

LONG SURVIVAL FOLLOWING CORONARY THROMBOSIS

E. H. Drake, M.D.
Portland, Me.

EXPERIENCE has taught us not to take an extremely pessimistic attitude regarding the outcome of coronary occlusion. Thirty years ago coronary thrombosis was a medical curiosity, known only to pathologists. After the belated recognition of Herrick's[1] observations, it was at first believed that hardly more than one-half of the patients survived the acute attack. Time has shown that this figure is far too high; we now believe that the immediate mortality of coronary thrombosis under the best conditions is about 15 per cent. The future of the survivors, however, is not as good as this. Statistics covering several large groups of patients show that the period of survival does not run much beyond two years.* If this be true, it would appear that our optimism must be confined, in the main, to the prognosis of the immediate attack. We might almost as well consider that such patients are permanently disabled and count it hardly worth while to attempt to return them to active life. The only ray of hope seems to be that a small percentage of survivors will make surprising recoveries and be able to live and work for a varying number of years. The attitude of the physician today, therefore, is that he must not be too depressed about the statistics of survival, for, occasionally, these patients do better than the average patient could be expected to do.

If specific questions are asked, it is not unusual to discover a history of previous coronary thrombosis. A number of five- to seven-year survivals have been reported. In a follow-up study of a large group of patients who had had coronary thrombosis, Conner and Holt[2] recorded the survival of one person for eighteen years after what, according to the history, appeared to have been coronary thrombosis. White,[3] in 1933, reported finding, at autopsy, a single scar in the heart of a man of 80 whose history suggested that he had had coronary thrombosis at the age of 63. This man had lived a vigorous life after his coronary occlusion and had been free from heart symptoms until he developed angina pectoris eleven years after the occlusion. The same author,[4] in 1937, reported the survival of a patient for more than twenty-four years after the first coronary thrombosis. There had been an interval of fifteen years' freedom from symptoms between the initial coronary thrombosis and a subsequent series of cardiac infarctions. In the case here reported, the patient enjoyed an even longer interval of freedom from symptoms and duration of life after coronary thrombosis.

Received for publication Dec. 14, 1939.

*The average duration of life in 101 cases of coronary thrombosis recently reported by Dr. Francis F. Rosenbaum, Peter Bent Brigham Hospital, Boston, was 41.1 months.

REPORT OF CASE

A telegrapher, whose age was 72 when he was first seen, March 29, 1933, had suffered from angina of effort for five years. He stated that he had experienced the same pain at the age of 40 years, except that at the earlier date the pain had been more severe, and that, over a period of a few weeks, it had gradually increased in intensity, had come at more frequent intervals, and had been more easily precipitated. Finally, an attack of pain did not subside within the usual time, and the administration of an opiate was twice required. He was confined to his bed for two weeks, and said that for another two weeks he felt weak and was unable to work. There was, however, no return of the pain during the next twenty-seven years, or until he had reached the age of 67. At the time of examination he had hypertension and cardiac enlargement. Jan. 15, 1935, he suffered a coronary thrombosis from which recovery was uneventful except for a complicating attack of arthritis. Following this attack the electrocardiogram showed left bundle branch block. He continued to have mild angina pectoris on rare occasions, and obtained easy relief from nitroglycerin. At the age of 77 he retired from his position. April 28, 1938, another coronary thrombosis occurred. This attack was severe, was accompanied by marked pulmonary edema, and was followed by frequent, severe recurrences of pain, and then by cerebral embolism and left-sided hemiplegia. He was confined to bed for four

Fig. 1.—Roentgenogram of heart opened by the Schlesinger method. Right auricle and ventricle situated on the side of the film on which marker is placed. The interventricular septum has been removed and is placed below the heart. The film has not been retouched.

months. Attacks of angina pectoris continued but were infrequent. He had developed prostatic hypertrophy, which caused nocturia, and, unless he was able to void promptly when he awakened in the night, an attack of angina pectoris would result. Because he feared the cardiac pain, he occasionally took nitroglycerin at these times to forestall an anginal attack. He was awakened at 3 o'clock in the

morning of Oct. 2, 1939, with a desire to void, and experienced an attack of angina pectoris which was not relieved by nitroglycerin. A hypodermic injection of morphine was ordered by telephone; a half-hour later he was unconscious, and died within a few minutes.

Before permission for autopsy could be obtained the body had been embalmed; for this reason the heart was considered unsuitable for injection studies. The heart weighed only 360 Gm. The organ was divided by the method of Schlesinger,[5] and a roentgenogram was made. The course of the main branches of the coronary arteries can be quite clearly followed in the roentgenogram, for they are outlined by patches of calcification. Old obstructions, with calcification, were found in the left anterior descending branch, a large branch of the left circumflex, and the right circumflex artery. There were three fair-sized areas of fibrosis in the ventricular walls; the most recent was in the posterior basal portion of the left ventricle. There was no fresh coronary thrombosis to explain the fatal attack.

It seems certain that one of the three scars had resulted from the myocardial infarction which this man had suffered at the age of 40. Following this illness he returned to his usual occupation, and continued to work for thirty-seven years, until he reached the age of 77. For twenty-seven years after his recovery he had no cardiac symptoms. At the age of 67 years he developed angina pectoris, as any man of this age might. When he was 75, another coronary thrombosis, producing bundle branch block, occurred. This illness did not seem to change his physical condition materially after the period of healing had taken place. Three years later he suffered a third coronary thrombosis and was desperately ill for many weeks, but finally recovered. He died rather suddenly from a nocturnal attack of angina pectoris in his eightieth year, nearly forty years after the initial infarction of the heart.

Since we have understood coronary thrombosis for so short a time, cases of long survival could not fall within the personal knowledge of any one physician. It would be necessary to depend upon the patient's history, and to have autopsy corroboration. Coronary thrombosis was formerly wont to masquerade as "acute indigestion," and its true nature was unknown to physician and patient alike. Therefore, a history such as this patient gave would be, of necessity, uncommon. It is suspected that certain middle-aged patients may recover completely from coronary thrombosis and live out their span of life, in spite of the present belief that life is of short duration after cardiac infarction.

REFERENCES

1. Herrick, J. B.: Clinical Features of Sudden Obstruction of the Coronary Arteries, J. A. M. A. **59**: 2015, 1912; and Thrombosis of the Coronary Arteries, J. A. M. A. **72**: 387, 1919.
2. Conner, L. A., and Holt, E.: The Subsequent Course and Prognosis in Coronary Thrombosis. An Analysis of 287 Cases, AM. HEART J. **5**: 705, 1930.
3. White, P. D.: Longevity After Coronary Thrombosis, J. A. M. A. **100**: 233, 1933.
4. White, P. D.: New Record in Longevity After Coronary Thrombosis, J. A. M. A. **108**: 1796, 1937.
5. Schlesinger, Monroe J.: An Injection Plus Dissection Study of Coronary Artery Occlusion and Anastomoses, AM. HEART J. **15**: 528, 1938.

TERMINAL CARDIAC MECHANISM IN CORONARY ARTERY DISEASE*

Report of Two Cases

Ben E. Goodrich, M.D., Detroit, Mich., and Robert J. Needles, M.D., St. Petersburg, Fla.

IN NOVEMBER, 1938, Grieco and Schwartz[1] demonstrated that ventricular standstill may be the cause of death after acute coronary artery thrombosis. They did not observe ventricular fibrillation following the ventricular tachycardia which preceded cardiac death. In June, 1939, F. Janney Smith[2] reported, from this clinic, a case in which ventricular fibrillation occurred after acute coronary artery thrombosis. It has been our singular experience to observe electrocardiographically, during one afternoon, the terminal cardiac mechanism in two instances of sudden death from coronary artery disease. One of these deaths was shown, at autopsy, to have been caused by marked coronary artery sclerosis (the patient had had angina pectoris). The other was undoubtedly the result of infarction of the anterior wall of the heart; it occurred on the tenth day following the coronary occlusion.

CASE REPORTS

Case 1.—A. J. A. (No. 79986), a white man, 46 years old, was first seen in June, 1926. On subsequent occasions, in the hospital and outpatient department, he had been treated for a number of minor complaints. No serious illness was noted until Aug. 2, 1939, when he stated that for several weeks he had had severe, aching pain in both shoulders and down both arms. The distress was periodic and would last only a few minutes. It was present only during exertion, and was relieved promptly by rest. It was most likely to occur after meals. There had been no substernal or precordial distress.

On Aug. 11, 1939, abut 3:00 P.M., the patient made one of his regularly scheduled visits to the outpatient department. He had been feeling well and had noted no distress or discomfort that day. In the lobby of the hospital he collapsed, became unconscious and cyanotic, and shortly vomited. He was brought to the cardiac clinic, where he recovered for a few moments and indicated that he was having crushing substernal pain. Concentrated glucose solution (100 c.c. of 20 per cent), with 3.5 grains (0.25 gram) of aminophyllin, was administered intravenously. He soon lapsed into complete coma. The ashen cyanosis increased. The cardiac rate was 54, and the beating was regular. The blood pressure could not be obtained, and the peripheral pulse was imperceptible. He was sweating profusely. An electrocardiogram was obtained. He was given 0.5 c.c. of adrenalin subcutaneously, and heat was applied externally. A pronounced protodiastolic gallop rhythm was present, together with irregularly occurring extrasystoles. The electrocardiograph was again connected. At about 3:15 P.M. a severe clonic convulsion occurred, and respirations ceased. The heart sounds could not be heard, and it was felt that the patient was dead. Artificial respiration was applied, and 1 c.c. of adrenalin was injected into the heart. No further evidence of life appeared except in the electrocardiogram (Fig. 1).

*From the Department of Medicine, Henry Ford Hospital.
Received for publication Nov. 27, 1939.

After 3:15 P.M., when, from the clinical standpoint, the patient was dead, the record first showed an almost regular heartbeat, at a rate of approximately 150, and complexes which varied slightly in contour. Three minutes later the complexes were smaller and varied more. At 3:20 and 3:21 there were prominent, rounded waves which occurred at a rate of 72; they were preceded and followed by very small deflections. At 3:22, there was, for a time, no evidence of ventricular activity, for

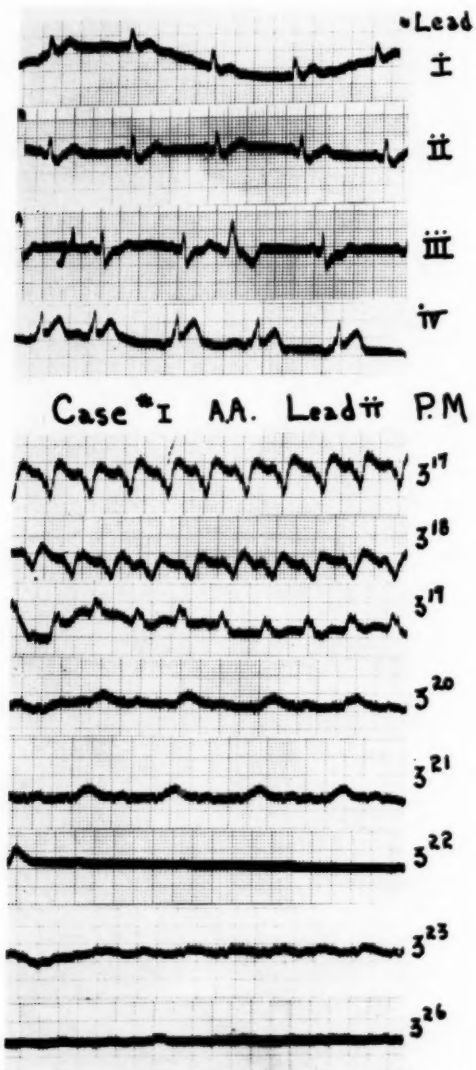


Fig. 1.

the small deflections which occurred at a rate of less than sixty a minute may have been entirely of auricular origin. With the resumption of ventricular activity, at 3:23, although the voltage was small, there continued to be a recurring similarity in the form of the complexes. The last portion of the record showed a further decrease in the amplitude of the deflections.

The autopsy was performed by Dr. G. B. Kerr. The left anterior coronary artery was tortuous and thickened, and the lumen was almost obliterated in several

places by confluent atherosclerotic plaques. No fresh thrombus could be seen. The right coronary artery showed only an occasional patch of atherosclerosis. No area of myocardial infarction could be demonstrated, either grossly or by histologic section.

This was an example, therefore, of sudden death from acute coronary insufficiency, in a case of advanced coronary artery disease. Death occurred within one-half hour after the onset of severe, prostrating pain. Ventricular fibrillation did not occur.

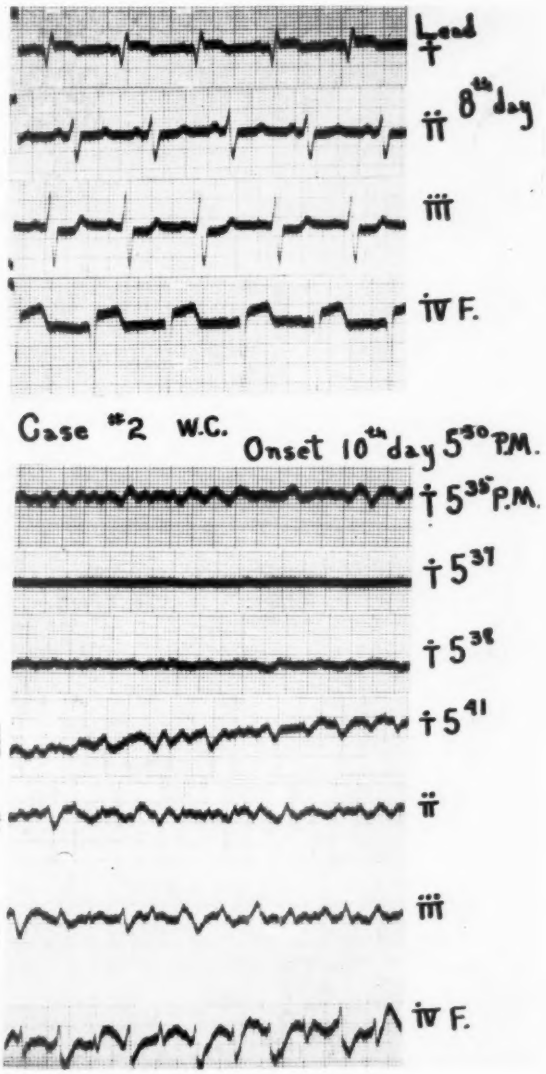


Fig. 2.

CASE 2.—Wm. C. (No. 7209), a 60-year-old man, was first seen in August, 1920. Gastrointestinal dysfunction, prostatic enlargement, and fatigability required treatment occasionally thereafter. In 1937, weakness and faintness occurred in brief attacks, and similar sensations were produced by stimulation of the carotid sinus. The electrocardiogram was normal except for slight left ventricular preponderance.

On July 31, 1939, the patient reported that the previous evening, when he was attempting to go to sleep, he noted a sensation of epigastric pressure, and substernal pain which radiated to the jaw. The sensation was transient, and was relieved by sitting up. After four or five attempts, the patient was able to recline comfortably, and slept well. It appeared probable that coronary thrombosis was impending, and the patient was admitted to the hospital, where he spent a comfortable night. No fever, tachycardia, or leucocytosis was present. The following day (Aug. 1, 1939), at 10:30 P.M., the patient suffered severe, continuous, precordial pain, for which he was given morphine, oxygen, and aminophyllin intravenously. The pain persisted, in lessening degree, for twelve hours. The following day the temperature reached 102.8° F. Gallop rhythm, a fall in blood pressure, electrocardiographic changes, and leucocytosis developed. Attacks of nocturnal pulmonary edema occurred despite the fact that the oxygen tent was employed continuously. The electrocardiogram which was made Aug. 9 is reproduced in Fig. 2.

On Aug. 11, at 5:30 P.M., the patient awakened from a restful sleep and suddenly became anxious, restless, and very dyspneic. Within a few seconds the pulse became imperceptible and the cyanosis extreme. The pulse promptly reappeared, and was very rapid; the heartbeat was thought to be regular, and the rate was in excess of 180 per minute. Within less than an additional minute the pulse again faded away, the heart sounds disappeared, cyanosis deepened, and a few gasping respiratory attempts were made. The patient appeared to be dead. An intracardiac injection of adrenalin and massage of the epigastrium had no effect.

The electrocardiograph was connected approximately five minutes after the onset. Sample sections from the continuous record were chosen for reproduction; the time intervals are approximate. The complexes were wide and diphasic, and occurred rapidly and irregularly (ventricular fibrillation).

A post-mortem examination was not permitted.

SUMMARY

A case is reported in which ventricular tachycardia was followed by cardiac standstill; the cause of death was coronary artery disease. This is in support of the contention of Grieco and Schwartz that cardiac standstill should occur as frequently as ventricular fibrillation, and that, if more records could be obtained, additional instances of cardiac standstill would probably be discovered.

A second case, in which ventricular fibrillation occurred during the period of terminal cardiac activity, is added to the five such cases which have been previously reported by others.

REFERENCES

1. Grieco, Emil H., and Schwartz, Sidney P.: Observations on the Mechanism of the Dying Heart in a Patient With Ventricular Tachycardia, AM. HEART J. **16**: 595, 1938.
2. Smith, F. Janney: Ventricular Fibrillation as a Cause of Sudden Death in Coronary Artery Thrombosis, AM. HEART J. **17**: 735, 1939.

Corrigendum

Attention is called to the republication of the article by Ben E. Goodrich, M.D., Detroit, Mich., and Robert J. Needles, M.D., St. Petersburg, Fla., "Terminal Cardiac Mechanism in Coronary Artery Disease" (**20**: 498, 1940), because of the omission of the last part of the article in the October issue, page 500. The complete article appears in this issue.

Department of Reviews and Abstracts

Selected Abstracts

Scupham, George W., DeTakats, Geza, Van Dellen, Theodore R., and Beck, William C.: Vascular Diseases. A Review of Some of the Recent Literature, With a Critical Review of the Surgical Treatment. Arch. Int. Med. 66: 707, 1940.

In these important annual reviews the authors do not attempt to include all of the available literature on vascular diseases. Many deserving articles have undoubtedly been missed, and consequently the reviews must not be considered complete. Preference was usually given to articles containing original ideas, as well as to those confirming or disproving existing beliefs. Many articles were included on merit alone, or their contents were thought worthy of repetition. The study of vascular diseases is not without its difficulties and is open to criticism. The vast amount of instrumentation is certainly unnecessary for diagnosis; in the majority of cases the history and findings alone are sufficient. Arteriosclerosis, the most prevalent vascular disease, has received too little attention.

This review is always "must" reading.

AUTHORS.

Collins, Dean A., and Hamilton, Angie S.: Pressor Responses Following Short, Complete Renal Ischemia: Characteristics, Mechanism, Specificity for Kidney. Am. J. Physiol. 130: 784, 1940.

Taquini's findings are confirmed; intervals of complete, bilateral renal ischemia of six to seven hours' duration invariably result in elevations of blood pressure when circulation is restored.

Briefer intervals of complete renal ischemia, even those as short as one-half hour, consistently give pressor effects. The magnitude of the responses is only slightly less than that from longer periods.

The characteristics of the response are as follows: The blood pressure rises gradually, reaching a maximum two to nine minutes after the release of the occluding clamps; the elevation is prolonged; in some cases the gradual rise is preceded by preliminary changes, consisting usually of a relatively rapid rise followed by a fall; these preliminary variations are not due to stimulation incident to opening the clamps; the gradual prolonged response is independent of the height of the initial blood pressure.

Occlusion and subsequent restoration of the blood supply of one kidney, either with the other intact or clamped, is followed by a prolonged elevation of blood pressure.

A nervous mechanism is not involved in these responses. This conclusion is based on four groups of experiments: (1) manipulation of the clamps; (2) opening of the clamps with the vessels of the kidney ligated and the accompanying nerve plexuses intact; (3) complete ischemia, with the kidneys and their vessels denervated; (4) complete ischemia, with the thoracolumbar cord destroyed and the vagi cut. The responses must, therefore, be due to pressor material from the ischemic kidney. This material does not exert its pressor action solely, if at all, through the central nervous system.

If the circulation to the leg or to a portion of the liver is arrested for about two hours, no elevation of blood pressure occurs when the circulation is restored.

Neither recent adrenalectomy nor recent splenectomy prevents an elevation of blood pressure following restoration of renal circulation after complete bilateral ischemia.

AUTHORS.

Weeks, David M., Steiner, Alfred, Mansfield, James S., and Victor, Joseph: The Depressor Effect of Spleno-Reno-Pexy on Hypertension Due to Renal Ischemia. J. Exper. Med. **72**: 345, 1940.

In hypertensive dogs with bilateral renal ischemia, unilateral splenorenopexy lowers the systolic blood pressure for as long as nine and one-half months.

Following removal of the fused spleen and kidney, the decreased blood pressure of the dogs with renal ischemia returns to the hypertensive level.

The splenorenopexy produces a collateral circulation between the splenic sinusoids and the capillaries about the renal tubules. The glomeruli are not usually involved in this collateral circulation.

AUTHORS.

Ornstein, George G., and Epstein, Israel G.: Spirometry as a Procedure of Determining Pulmonary Efficiency in Pulmonary and Heart Disease. The Failure of X-rays of the Chest in Estimating Pulmonary Reserve. J. M. Soc. New Jersey **37**: 401, 1940.

The use of spirometry is advocated as a simple method of estimating pulmonary reserve and efficiency in cardiac and pulmonary diseases.

By means of spirometry the predicted maximum minute ventilation may be calculated from the actual vital capacity. A formula has been developed to calculate the pulmonary reserve compared to the resting minute ventilation. The normal is a reserve that is ten times greater than the resting minute ventilation.

When the pulmonary reserve is less than six times the resting minute ventilation, symptoms of anoxemia occur. Dyspnea is the chief symptom, and it increases in intensity as the pulmonary reserve falls.

When the maximum minute ventilation (pulmonary reserve) becomes less than four times the resting minute ventilation, the prognosis as to life is bad.

The measured minute ventilation is higher than the calculated normal when the maximum ventilation is reduced in volume.

The roentgenogram of the lungs cannot be used in estimating pulmonary reserve.

AUTHORS.

Holt, J. P.: The Measurement of Venous Pressure in Man, Eliminating the Hydrostatic Factor. Am. J. Physiol. **130**: 635, 1940.

Venous pressure was determined in the supine and prone positions in ten normal subjects, using a modification of the direct method of Moritz and Tabora. Venous pressure values obtained using the reference point of Moritz and Tabora and that of Eyster were markedly different from the values obtained using the reference points of von Recklinghausen, Lyons et al., and the method described here. The reference point of Moritz and Tabora and that of Eyster appear to be placed too far ventrally.

It is suggested that venous pressure be determined in the following manner in order to eliminate the hydrostatic factor. The pressure in the antecubital vein

is measured by the direct method, with the subject in the supine position, the arm lying well below the center of the body and abducted to approximately 45°. The subject is turned over into the prone position and the pressure is measured again, with the arm well below the center of the body and abducted to about 45°. All pressures are referred to the level of the spine as zero. The sum of the two pressures divided by two equals the venous pressure, and the reference point is located at the point in the chest midway between the tops of the two columns of saline in the two pressure measurements.

Venous pressure determined in this manner varied between 7.8 and 14.1 cm. of saline, with results in 80 per cent of the cases varying between 7.8 and 12.1 cm. of saline.

AUTHOR.

Altschule, Mark D., Volk, Marie C., and Henstell, H.: Cardiac and Respiratory Function at Rest in Patients With Uncomplicated Polycythemia Vera. Am. J. M. Sc. **200**: 478, 1940.

Measurements of cardiac and respiratory function in patients with polycythemia vera at rest are normal.

The slowing of blood flow, and the symptoms associated with it, are not due to impaired cardiac function but rather to increased resistance to the flow of blood through the small capillaries. This is largely due to increased viscosity of the blood.

AUTHORS.

Arrighi, Federico P.: A New Type of Membrane for Direct Phonocardiography. Rev. argent. de cardiol. **7**: 82, 1940.

A new type of membrane for direct phonocardiography is described. It is made of elastic collodion (solution of pyroxilin in alcohol and ether). Once applied on the segmented capsule, it is wrinkled to make it more sensitive and aperiodic.

The membrane thus prepared has good sensitivity, is well dampened, gives good tracings with scarcely any distortion, and may last for years.

AUTHOR.

Buchbinder, W. C., and Sugarman, H.: Arterial Blood Pressure in Cases of Auricular Fibrillation, Measured Directly. Arch. Int. Med. **66**: 625, 1940.

The blood pressure has been recorded in cases of auricular fibrillation in man by a direct method.

Fluctuations of blood pressure occur from beat to beat in cases of auricular fibrillation and other irregularities of the heart. The systolic and pulse pressure show a direct relation and the diastolic pressure an inverse relation to the preceding cycle length.

The QE interval was measured and found to shorten with the longer cycle lengths.

The duration of ejection fits the formula $S = K \sqrt{C}$, and in four of our cases in which a curve of means could be drawn, K equaled 0.26, 0.26, 0.26, and 0.23.

In cases of auricular fibrillation and flutter with regular rhythm, the values for blood pressure are nearly constant.

Extrasystoles are found to obey the same relation to the preceding cycle length as that found with auricular fibrillation and flutter, but in their presence additional factors play some role.

These results confirm and extend results obtained with the experimental animal and those in man based on accurate recording of the pulse. They indicate the pulse pressure determines pulse amplitude and that pulse contour is a mirror of the variations in internal pressure during the cardiac cycle at the site where the pulse is recorded.

The results definitely show that it is impossible to obtain accurate determinations of blood pressure by any of the indirect methods when the pulse is grossly irregular.

AUTHORS.

Tinney, W. S., Jr.: Interauricular Septal Defect. Arch. Int. Med. 66: 807, 1940.

Two cases of uncomplicated interatrial septal defect are presented. The respective ages of the patients were 76 and 47.

A review of the literature since 1934 has revealed 22 cases of interatrial septal defect. Roesler's review in 1934 included 62 cases. This brings the total number of cases reported to 86, including the 2 reported here.

The characteristic pathologic features in addition to the septal defect are marked hypertrophy and dilatation of the right auricle, the right ventricle and the pulmonary artery. The left auricle, the left ventricle and the aorta are all relatively small.

The only way to be sure of a correct diagnosis is by roentgen or fluoroscopic examination. There are four characteristic features: increased hilar shadows, great enlargement of the right side of the heart, a small aortic knob and a very large pulmonary conus.

AUTHOR.

Myers, Victor, and Mangun, George H.: Some Chemical Observations on the Human Heart in Health and Disease. J. Lab. & Clin. Med. 26: 199, 1940.

This report deals largely with a discussion of the chemical composition of the heart muscle itself and some of the factors that had been found to influence it. The chemical deficiencies of the myocardium associated with, or resulting from, myocardial insufficiency must constitute limiting factors in the process of recovery. A decompensated heart, although it may be capable of performing a limited amount of work sufficient to maintain the patient in a state of rest, cannot be considered to have recovered, from a chemical point of view, until a complete restitution of the chemical mechanism has been effected.

The chemical substances discussed in this paper by no means encompass the whole realm of possibilities. The number and variety of compounds concerned with the metabolism of the heart are expanding constantly, and new facts are being uncovered which throw light upon the question of how carbohydrates, fats, and proteins, their intermediate products, both in aerobic and anaerobic conditions, supply the energy of contraction. It is indeed possible that somewhere along the way we shall uncover information leading to a direct attack upon the complex problem of myocardial failure.

AUTHORS.

Ernstene, A. Carlton, and Kinell, Jack: Pain in the Shoulder as a Sequel to Myocardial Infarction. Arch. Int. Med. 66: 800, 1940.

The development of persistent pain in one or both shoulders is a relatively common sequel to myocardial infarction. The severity of the condition ranges from the clinical picture of typical periarthritis with intense pain and great limitation of motion to one of mild aching pain with a sensation of weakness but without loss of function. The left shoulder is affected more commonly than the

right, and the symptoms persist for several weeks or months. In a few patients, changes similar to those of rheumatoid arthritis develop in other joints either simultaneously with, or subsequent to, the appearance of the symptoms in the shoulder.

The present report is based on seventeen cases of persistent pain in the shoulder region encountered in a series of 133 consecutive cases of myocardial infarction. In fifteen of these the pain dated from the attack of coronary occlusion or developed subsequent to the attack. In the other two, the patients had suffered from angina pectoris and practically constant pain in both shoulders for a long time before the acute coronary attack. In both of them the pain in the shoulder increased in severity after the occurrence of myocardial infarction. In six of the seventeen cases symptoms of rheumatoid arthritis involving other joints developed either simultaneously with or subsequent to the appearance of the symptoms in the shoulder.

After the severe pain of coronary occlusion, certain patients for a long time may unconsciously keep the muscles of the shoulder girdle on one or both sides in a state of abnormal tension as a protecting mechanism against the possible recurrence of pain. Tension of this kind might be expected to be greater on the side to which the pain of the coronary seizures radiated, and this theory would help to explain the relation between the direction of radiation of the cardiac pain and the site of the subsequent persistent symptoms in the shoulder. Once the pain has appeared in the shoulder, continued tensing of the muscles would be natural, and this tension in turn would explain the prolonged duration of the symptoms in so many patients. As matters stand at present, however, there is not sufficient evidence to enable one to state which of the above mechanisms is actually responsible for the development of the persistent pain.

The practical significance of this sequel to myocardial infarction is pointed out.

AUTHORS.

Bourne, Geoffrey: Spontaneous Pneumothorax Simulating Coronary Disease. Brit. M. J., p. 313, Sept., 1940.

Artificial pneumothorax is one of the conditions which clinically may simulate coronary disease. The two cases of spontaneous pneumothorax here described were regarded as being cardiac when first seen. One gave a clinical picture practically indistinguishable from that of coronary infarction, and the other, a picture very much like that of angina of effort.

In the absence of electrocardiographic and radiographic assistance, the diagnosis in such cases may be extremely difficult, for a small partial pneumothorax often gives rise to very slight signs, or to none at all. If the electrocardiograph is the only special means of investigation available, certain other facts tend to complicate the problem; for some cases of coronary disease show no abnormality in Leads I, II, and III, and this is revealed only if a tracing of Lead IV is taken. Again, it is possible for slight coronary infarction to occur even with a normal tracing of Lead IV, either because the lesion is in a "silent" area or because it is of small size. Moreover, in some patients with angina of effort the tracing in all leads is normal at first, although later changes may appear. An additional difficulty is the fact that pneumothorax, probably by rotating the cardiac axis, may produce electrocardiographic abnormalities suggesting coronary disease. These are most commonly T-wave abnormalities, S-T deviation from the isoelectric level, and absent or greatly reduced positive initial deflection in the standard Lead IV electrocardiogram.

AUTHOR.

Strauss, Sidney: Delayed Electrocardiographic Changes in Coronary Occlusion. Am. J. M. Sc. **200**: 474, 1940.

Five cases are reported in which the diagnosis of coronary occlusion was clear clinically from the start, the electrocardiograms showing changes only after a lag of several days. In one instance the changes were minimal and not definitely diagnostic without the patient's history.

An adequate history is all-important in the diagnosis of coronary occlusion, as in all diseases. The diagnosis cannot be left to the cardiographic laboratory alone, but must be made by the clinician on the basis of all the available data. Negative or inconclusive electrocardiographic findings do not exclude the presence of a coronary occlusion.

AUTHOR.

Crimm, Paul D., McDonald, J. D., and Cookson, Howard N.: Calcification of Pericardium. J. Indiana M. A. **33**: 415, 1940.

A case is presented of a boy, aged 12 years, who had an adhesive pericardium, with marked calcium deposition. The etiological infection was probably pneumococcic. An atypical Pick's syndrome was observed; cirrhosis of the liver was present, with ascites of the abdomen and scrotum, but no edema of extremities. Operative relief was demonstrated to be impossible because of the extensive shell of calcium enveloping the heart.

AUTHORS.

Drummond, C. I.: Calcification of Pericardium. Northwest Med. **39**: 217, 1940.

Chronic constrictive pericarditis is not an extremely rare disease, but it is one of the most difficult cardiac conditions to diagnose, due to the lack of uniformity of signs and symptoms. There are certain clues that will lead us to a correct diagnosis.

One case of chronic constrictive pericarditis with calcification is reported, in which diagnosis was made before death. One of the unusual symptoms in this case was edema of the head and neck present in the morning, which subsided after the patient had been sitting up for a few hours.

AUTHOR.

Levitt, Abel, and Jaskiewicz, Stanley J.: Rheumatic Heart Disease. Am. J. Clin. Path. **10**: 467, 1940.

The authors have reviewed 110 cases of patients with rheumatic heart disease who have come to autopsy, 58 per cent of whom gave no history of having had rheumatic or antecedent upper respiratory tract infections. A similar percentage died under the age of 50 years. Subacute bacterial endocarditis was observed in 17 per cent of the cases, while syphilitic mesoaortitis complicated the endocarditis in 8 per cent of the cases. In two cases the three types of heart disease—chronic endocarditis, syphilitic mesoaortitis, and subacute bacterial endocarditis—were present.

AUTHORS.

Symonds, C. P.: Cerebral Thrombophlebitis. Brit. M. J. p. 348, Sept., 1940.

Mitral stenosis can be diagnosed in a high percentage of cases by careful roentgenologic examination, including fluoroscopy.

The demonstration of a calcified mitral valve is unequivocal evidence of mitral stenosis and also indicates its rheumatic etiology.

Dilatation of the left auricle without general cardiac enlargement is highly presumptive evidence of mitral stenosis.

The diagnosis of mitral stenosis can be made at times by roentgenologic examination, even in the absence of characteristic physical signs herein called "subclinical mitral disease."

AUTHOR.

Altschule, Mark D., and Budnitz, Edward: Rheumatic Disease of the Tricuspid Valve. Arch. Path. **30**: 7, 1940.

The clinical syndrome of rheumatic disease of the tricuspid valve is characterized by distention and increase in diameter of all visible veins, hepatomegaly, systolic (and in the absence of auricular fibrillation, presystolic), venous and hepatic pulsations, cyanosis, jaundice, enlargement of the heart to the right, and murmurs over the area of the tricuspid valve. The clinical evidence of cirrhosis of the liver or of congestive heart failure may complicate the picture. The special pathologic condition causing this syndrome consists in insufficiency and variable degrees of stenosis of the tricuspid valve, dilatation of the right auricle and of the veins, and cirrhosis of the liver. The cardiac output is normal when congestive failure is not present. Nevertheless, the venous pressure is elevated, proving that the rise in pressure is due to mechanical obstruction to the heart's inflow of blood. When cardiac decompensation occurs, the output of the heart diminishes and the venous pressure rises above its former high level. The relation of the pathologic and physiologic features of the syndrome to its clinical manifestations is discussed in detail.

AUTHORS.

Stickney, J. Minott, and Keith, Norman M.: Renal Involvement in Disseminated Lupus Erythematosus. Arch. Int. Med. **66**: 643, 1940.

The visceral involvement in disseminated lupus erythematosus has been reviewed clinically. The pathologic changes in the kidneys in fifteen fatal cases have been studied. In eight of the fifteen cases there was no definite renal change except that seen terminally in debilitating disease. Without exception, the weight of the kidneys was normal or greater than normal. No contracted kidneys were found.

The most definite lesion was a proliferation of the endothelial cells of the glomerular capillaries. Hyaline thickening of these capillary walls and an irregularity and thickening of the basement membrane were also frequently present. These changes are somewhat similar to those which have been described in acute glomerulonephritis and the toxemias of pregnancy. In one case in this series (Case 15) there were pathologic changes characteristic of glomerulonephritis. The relationship of the changes noted to the lupus erythematosus is uncertain, since the renal disease preceded the cutaneous and the cutaneous lesions were inactive during the final illness. In one other instance (Case 4) there was some evidence of a subacute or early chronic glomerulonephritis. In this patient, too, the evidence of renal damage was known to have antedated the onset of the cutaneous lesions. The arteries and arterioles were normal in most of the cases. In several there was slight thickening of the intima, but no thromboses were seen. The changes in the tubules were of a minor nature.

AUTHORS.

Weatherby, Lt. Colonel F. E., and Wiley, Capt. N. H.: Left-Sided Weakness, Blood Pressure Difference Between the Two Arms and Left Optic Atrophy: A New Clinical Syndrome. J. Nerv. & Ment. Dis. **92**: 151, 1940.

An unusual syndrome, consisting of left optic atrophy, blood pressure difference between the two arms, and marked weakness of the left arm and left leg, together with slight weakness of the muscles of the right side of the face and the left side of the tongue, is described.

There was no record or history of syphilis, and both blood and spinal fluid were repeatedly negative.

General arteriosclerosis and renal failure to concentrate were present.

There was no clinical or roentgenologic evidence of intrathoracic tumors, aneurysm, or coarctation of the aorta.

Left-sided weakness was greatly ameliorated by the use of a glass suction boot.

Possibilities of an unusual distribution of arteriosclerosis and of an unknown disease of the brain are suggested.

AUTHORS.

Braun-Menendez, E., Fasciolo, J. C., LeLoir, L. F., and Muñoz, J. M.: The Substance Causing Renal Hypertension. J. Physiol. **98**: 283, 1940.

The pressor and vasoconstrictor properties of the venous blood from kidneys in acute ischemia have been studied. Extracts of this blood contain a pressor substance (hypertensin) which is also formed in vitro when blood proteins are incubated with renin.

Some chemical and pharmacologic properties of hypertensin have been studied and found to be different from those of other known substances.

Experiments are reported which indicate that renin is an enzyme, blood pseudoglobulins the substrate, and hypertensin the reaction product. Hypertensin disappears if the reaction is permitted to go too far, and it is also inactivated by other proteolytic enzymes and by blood.

The pressor action of renin appears to be due to the formation of hypertension in blood; and a similar mechanism is suggested for arterial hypertension due to renal ischemia.

AUTHORS.

Crabtree, E. Granville: Pyelonephritic Injuries to the Kidney and Their Relation to Hypertension. J. Urol. **44**: 125, 1940.

A high percentage of pregnancy pyelonephritis patients show evidences of renal damage after five to eighteen years. The renal insufficiency had not progressed to the point of elevated nonprotein nitrogen in but one of the cases studied, the case of toxemia and pyelonephritis.

Hypertension was present in eight of seventy-two cases of pyelonephritis and in all of those that were complicated by toxemia. The relation of hypertension to the degree of renal damage was not always constant, but there was a closer relation of hypertension to the cases which showed marked renal insufficiency than to those which showed lesser degrees of damage to the kidneys. Hypertension is not the rule in cases of pyelonephritis pregnancy at from five to eighteen years after the infection.

Many of the patients studied appeared to be in excellent health.

AUTHOR.

Palmer, Robert S., Chute, Richard, Crone, Neil L., and Castleman, Benjamin: The Renal Factor in Continued Arterial Hypertension Not Due to Glomerulonephritis, as Revealed by Intravenous Pyelography. New England J. M. 223: 165, 1940.

Forty-seven (22 per cent) of 212 patients with continued arterial hypertension not due to glomerulonephritis showed congenital or acquired deformities of the pelves or ureters by urography.

The deformity in the pyelogram was unilateral in thirty-four (72 per cent) of these forty-seven cases, or 16 per cent of the 212 cases studied.

Such deformities are often incidental, but if significant in the etiology of the hypertension, probably represent a participating or precipitating rather than a major factor.

Surgical removal of the presumably offending organ in nine cases resulted in marked improvement in the blood pressure and the symptoms for one year and ten months in one case, although this patient still remains definitely hypertensive.

In cases of unilateral renal disease associated with persistent hypertension, the decision to remove the affected kidney, with the hope of curing or modifying the course of the hypertension, is based on three assumptions: that the lesion is not incidental; that there is no vascular disease in the remaining kidney; and that one will not be faced with recurrent pyelitis in the remaining kidney.

AUTHORS.

Ochsner, Alton, and DeBakey, Michael: Peripheral Vascular Disease. Surg., Gynec. & Obst. 70: 1058, 1940.

The bases for rational therapy in peripheral vascular disease are discussed.

Peripheral vascular disease merely signifies a disturbance or actual diminution in the normal amount of circulating blood to a part and is usually the result of a varying diminution in the normal caliber of the peripheral vessels. This decrease in intraluminary volume may be caused by obliterative structural change, by abnormal spasticity, or by both, depending upon the type and stage of the disease.

Effective therapy aims at improvement in circulation or increase in blood supply to the part; this cannot be accomplished by an attack upon vessels that have already undergone structural change. Vasospasm, on the other hand, is a physiologic or functional derangement which can be influenced satisfactorily by appropriate therapy.

Because vasospasm is the one controllable factor, the determination of its presence or absence and its extent are of decisive importance.

Therapeusis in peripheral vascular disease consists of measures aimed to improve the peripheral circulation and may be divided into two large groups: (1) conservative measures; and (2) radical procedures.

Conservative measures are indicated in all cases of peripheral vascular disease except in acute vascular catastrophes and in the rapidly progressive peripheral vascular disturbances. The conservative measures consist largely of two groups: (1) those which are directed toward the elimination of all factors which increase vasospasm; and (2) those factors which produce vasodilatation. Of the former, emotional disturbances, environment, and tobacco are the most important. Of the latter, application of heat and rugs and the performance of vascular exercises are the most significant.

Whereas many of these conservative measures are justified and are usually sufficient to produce complete relief of symptoms, in the rapidly progressive case, and especially in the case associated with a prominent degree of vasospasm, at-

tack upon the sympathetic nervous system is considered desirable. The concept that in these vasospastic states, sufficient vasoconstrictor impulses are transmitted over the sympathetic pathways to cause diminished circulation and that the release of these impulses may be enough to permit the return of circulation to normal forms the rational basis for sympathectomy. Interruption of impulses over sympathetic pathways may be accomplished by chemical block or by resection.

Chemical block of the regional sympathetic ganglia in peripheral vascular disease is considered a conservative procedure because of its efficacy, its simplicity and facility of performance, and its economic advantages.

In the presence of marked vasospasm in patients with impending vascular catastrophes or in those in whom conservative measures fail to relieve the vascular manifestations, radical therapy is justified. Sympathetic denervation of the affected part, however, should be performed only after the demonstration of vasodilatation following the diagnostic test of procaine hydrochloride block.

The factors which have been considered for the comparative failure of cervicothoracic sympathectomy to maintain chronic vasodilatation are reviewed and analyzed critically.

The technical considerations in the performance of cervicodorsal and lumbar sympathectomies for peripheral vascular disease are reviewed historically, described, and illustrated.

AUTHORS.

Symonds, C. P.: Cerebral Thrombophlebitis. Brit. M. J. 2: 348, 1940.

In all except one of the cases related in this paper, visible proof of the diagnosis of thrombophlebitis was lacking. The clinical symptoms, however, exactly resemble those which have been recorded in cases (most of them following lateral sinus thrombosis from otitis media) in which the diagnosis has been proved post mortem. It appears probable that cerebral thrombophlebitis by direct extension from an infective source or occurring as part of a generalized tendency to thrombophlebitis is not very uncommon and frequently runs a benign course. Such cases in the past may have been erroneously attributed to arterial thrombosis or embolism, or to encephalitis. Some, especially those in which the onset accompanied focal epileptic attacks, have doubtless been diagnosed as meningitis or abscess. The latter diagnosis has led occasionally to unnecessary and probably harmful operation. In Case 4 the diagnosis was so much in doubt that it needed an exploratory craniotomy to satisfy physician and surgeon that the patient would make a spontaneous recovery. For these reasons, and in the hope that they may stimulate further inquiry, it has seemed worth while to record these few observations.

AUTHOR.

Steinberg, Israel, Robb, George P., and Roche, Ursula J.: The Differential Diagnosis of Mediastinal Tumor and Aortic Aneurysm. Value of Contrast Cardiovascular Visualization. New York State J. Med. 40: 1168, 1940.

Four cases are described which illustrate the practical value of visualization of the intrathoracic blood vessels in the differential diagnosis of aneurysm and tumor of the mediastinum. A metastatic carcinoma in the right side of the mediastinum and a primary sarcoma in the left side strikingly simulated aneurysm of the ascending and descending portions of the aorta, respectively. Visualization of the great blood vessels, however, revealed or confirmed the presence of aortic aneurysm in the latter cases and excluded intrinsic gross abnormality of the aorta in the other two instances.

AUTHORS.

Bourne, Geoffrey: Examination of the Heart in Recruits. Brit. M. J. **2**: 442, 1940.

The routine examination by the medical boards of many healthy young men called up for military service has brought into prominence various physical signs and symptoms referable to the heart. These are often slight, but their presence raises questions as to whether they can be ignored or whether they are important enough to justify the rejection of the man as unfit for service or his relegation to an inferior physical category.

Cases met with can be divided into three groups:

1. The heart is normal in size and shape when examined radiologically; no symptoms are present, but minor variations in the heart sounds cause suspicion of disease.

2. The heart is normal clinically and radiologically, but the history or symptoms suggest present or potential effort syndrome or neurocirculatory asthenia. These men, if passed for full active service, are likely to break down and to become a prolonged and severe charge upon the community and upon themselves. An attempt should be made to pass the slighter cases for clerical or other nonviolent work, or to find them official work similar to that which occupies them in civil life.

3. Exercise tolerance is normal, but physical abnormalities of the heart, either congenital or acquired, are detected. The diagnosis of the more common congenital abnormalities is described and an attempt is made to indicate the manner of dealing with the organic cases.

AUTHOR.

Flaxman, Nathan: Pregnancy and Heart Disease. Am. J. Obst. and Gynec. **39**: 814, 1940.

An analysis of the life cardiac histories of forty-nine women with organic heart disease who delivered from one to twenty-two children (average 4.9 pregnancies) as compared with the histories of forty-one nulliparous women with similar cardiac lesions, revealed that there was little or no difference in the known duration of the heart condition, in the ages at the onset of myocardial failure, or in the ages at death.

The heart lesions were recognized earlier in the parous women, mainly because of the pregnancies. In women with compensated rheumatic heart disease, pregnancy may be undertaken without any added risk. However, it is suggested that women with compensated heart disease be advised to marry early and bear children before the age of 25, if they desire a minimum of risk. In this way, also, they can have a longer period in which to rear their children. Women with heart disease die early because of the natural evolution of the cardiac disturbance and not because of the childbearing.

AUTHOR.

Brown, Clark E., and McNamara, Delbert H.: Acute Interstitial Myocarditis Following Administration of Arsphenamines. Arch. Derm. and Syph. **42**: 312, 1940.

A case of acute interstitial myocarditis complicating exfoliative dermatitis due to neoarsphenamine is reported. A similar case is reviewed in some detail, bringing the total cases reported to eight.

The probably allergic etiology of the myocarditis is discussed, although the exact nature of the allergen is not apparent.

AUTHORS.

Book Review

ATLAS OF CARDIOROENTGENOLOGY: By Hugo Roesler, M.D., Associate Professor of Roentgenology, Temple University School of Medicine, Philadelphia, 124 pages, 166 figures, Charles C. Thomas, Springfield, Ill., 1940. $8.50.

Superficially, the atlas method of presenting the subject of roentgenologic diagnosis appears to be an ideal one, yet it has not been notably successful in the past. In large part, this is because of the impossibility of illustrating even a small percentage of the innumerable variations in the roentgenographic appearance of the normal and pathologic anatomy of any structure. If one is to understand roentgenology, certain rules must be learned and certain details mastered. The temptation to interpret one roentgenogram in terms of another, seen on a previous occasion, or illustrated in a book, is strong enough; the possession of an atlas may, unfortunately, encourage this type of "snapshot" diagnosis.

With respect to diseases of the heart, these strictures are much less applicable, particularly in the case of this atlas. If used properly, that is, as a supplement to the author's text on the roentgenologic diagnosis of cardiac diseases, this volume should prove most valuable. A series of cases is presented, for each of which there are a well-written summary; reproductions of the roentgenograms; in many instances, photographs of the anatomic specimen; and many well-conceived diagrams to illustrate the normal and abnormal heart. Almost all of the various types of cardiac abnormalities are exhibited, and the discussions are sufficiently detailed to bring out the vital points in roentgenologic diagnosis. The author has described, very clearly, the anatomic relationships of the heart, the significance of the various curves and borders which are seen in the roentgenogram, and the effect of the pathologic physiology of cardiac disease upon the roentgenogram. In many respects, the comparison of the roentgenogram with the unique coronal dissections of the heart is the most valuable contribution of the atlas.

The format and printing are unusually fine, but the many expanses of blank white paper give an uncompleted appearance which is disturbing. Considering the size and cost of the atlas, 166 figures seem scarcely adequate. Although certain disease processes are well elaborated, notably the effects of emphysema upon the heart, the number of illustrations for the majority of cardiac lesions is insufficient. The demonstration of a case of "funnel" chest, without indication of the characteristic displacement of the heart to the left, is an omission. The textual material itself leaves nothing to criticize. Both the cardiologist and the roentgenologist will benefit greatly from a careful and repeated study of this splendid addition to the library of works on diseases of the heart.

LEO G. RIGLER

Announcement

Beginning January 1, 1941, the yearly subscription price of the AMERICAN HEART JOURNAL (two volumes) will be as follows: United States, its Possessions, and Pan-American Countries, $10.00; Canada, $11.50 (in Canadian currency); and Foreign Countries, $11.00. The price of journal membership in the American Heart Association will be raised from $10.00 to $11.00 per annum. These changes will not affect subscriptions or American Heart Association journal memberships which are already in force, but will apply to all new subscriptions and to renewals.

These increases have been made necessary by rising costs of production, but they will also enable the publisher to increase the size of each issue by sixteen pages, which will add a total of 192 pages to the two annual volumes. It is earnestly hoped that this additional space will make it possible to reduce to six months, or less, the interval between the receipt of manuscripts and their appearance in print.

American Heart Association, Inc.

RADIO CITY

1790 BROADWAY, NEW YORK, N. Y.

DR. WILLIAM D. STROUD
President

DR. PAUL D. WHITE
Vice-President

DR. HOWARD B. SPRAGUE
Secretary

DR. WALTER W. HAMBURGER
Treasurer

BOARD OF DIRECTORS

DR. T. HOMER COFFEN	Portland, Ore.	*DR. EDWIN P. MAYNARD, JR.	Brooklyn
DR. CLARENCE DE LA CHAPELLE	New York City	DR. THOMAS M. McMILLAN	Philadelphia
DR. WILLIAM DOCK	San Francisco	DR. JONATHAN MEAKINS	Montreal
DR. HUGH FARRIS	St. John, N. B., Canada	*DR. FRANKLIN NUZUM	Santa Barbara
DR. WALTER W. HAMBURGER	Chicago	DR. STEWART R. ROBERTS	Atlanta
DR. GEORGE R. HERRMANN	Galveston	*DR. ROY W. SCOTT	Cleveland
*DR. EMMET F. HORINE	Louisville	*DR. HOWARD B. SPRAGUE	Boston
DR. T. DUCKETT JONES	Boston	*DR. WILLIAM D. STROUD	Philadelphia
*DR. EMANUEL LIBMAN	New York City	DR. LOUIS VIKO	Salt Lake City
DR. DREW LUTEN	St. Louis	*DR. PAUL D. WHITE	Boston
DR. GILBERT MARQUARDT	Chicago	DR. FRANK N. WILSON	Ann Arbor
*DR. H. M. MARVIN	New Haven	*DR. IRVING S. WRIGHT	New York City
		DR. WALLACE M. YATER	Washington, D. C.

DR. H. M. MARVIN, *Chairman, Executive Committee and Acting Executive Secretary*

GERTRUDE P. WOOD, *Office Secretary*

TELEPHONE CIRCLE 5-8000

THE American Heart Association stands alone as the national organization devoted to educational work relating to diseases of the heart. Its Board of Directors is composed of twenty-five physicians representing every portion of the country.

The Section for the Study of the Peripheral Circulation was organized in 1935 for the purpose of stimulating interest in investigation of all types of diseases of the blood and lymph vessels and of problems concerning circulation of blood and lymph. Any physician or investigator in good standing may become a member of the section after election to the American Heart Association and payment of dues to that organization.

To coordinate and distribute pertinent information, a central office is maintained, and from it issues an ever widening stream of books, pamphlets, charts, posters, films, and slides. These activities all concern the recognition, prevention or treatment of the leading cause of death in the United States, diseases of the heart. The AMERICAN HEART JOURNAL is under the editorial supervision of the Association.

The income from membership and donations provides the sole support of the Association. Lack of adequate funds seriously hampers more widespread educational and research work imperative at this time. Great progress has been made, but much remains to be done.

Annual membership is $5.00 a year and journal membership at $10.00 includes a year's subscription (January-December) to the AMERICAN HEART JOURNAL and annual membership in this Association. A cordial invitation to join in this crusade is extended to you.

The American Heart Association solicits your support to the end that it may continue more effectively the campaign to which it has devoted all its energy.

**Executive Committee.*